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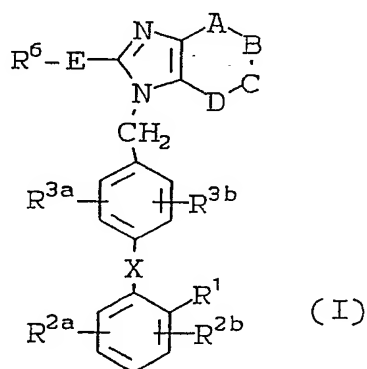
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B551 B552 B56Y B565 B566 B57Y B575 B576
B58Y B586 B59Y B595 B64Y B640 B65Y B650
B654 B656 B66Y B661 B67Y B670 B674 B823
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(54) **Substituted imidazo-fused 6-membered carbocycle or heterocycle as neurotensin antagonists**

(57) Treating disease states mediated by neurotensin by administering to a patient in need of treatment a therapeutically effective amount of a neurotensin antagonist which is useful against GI and CNS disorders which is a substituted imidazo-fused 6-membered carbocycle or heterocycle of structural formula I as disclosed in EP-0400974-A2 and EP-0400835-A2:



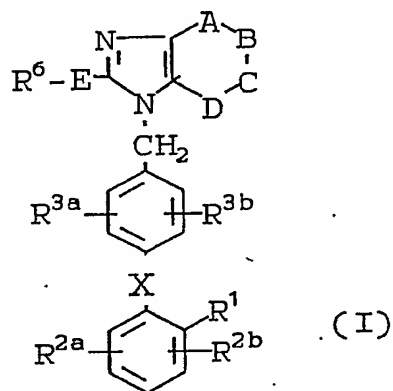
wherein A, B, C, and D are independently carbon atoms or nitrogen atoms.

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5 SUBSTITUTED IMIDAZO-FUSED 6-MEMBERED CARBOCYCLE OR
HETEROCYCLE AS NEUROTENSIN ANTAGONISTS

10 INTRODUCTION OF THE INVENTION

This invention is concerned with a method of
treating disease states mediated by neurotensin by
the administration to a patient in need of treatment
of a therapeutically effective amount of a
neurotensin antagonist which is a substituted
15 imidazo-fused 6-membered carbocycle or heterocycle of
structural formula I:



wherein A, B, C, and D are independently carbon atoms
30 or nitrogen atoms.

As neurotensin antagonists these compounds find utility in the treatment of CNS dysfunctions such as psychoses, depression, cognitive dysfunction, such as Alzheimer's disease, anxiety, tardive dyskinesia, drug dependency, panic attack and mania. The neurotensin antagonist property also imparts to the compounds utility in GI disorders such as gastroesophageal reflux disorder (GERD), irritable bowel syndrome, diarrhea, cholic, ulcer, GI tumors, dyspepsia, pancreatitis, esophagitis and gastroparesis. The known ability of neurotensin to release mast cell histamine indicates that antagonists will be useful in the treatment of allergic and inflammatory conditions.

BACKGROUND OF THE INVENTION

Neurotensin (NT) is a tridecapeptide hormone (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH), originally isolated from the bovine hypothalamus [Carraway, R. and Leeman, S. E., J. Biol. Chem., **248**, 6854 (1973)], has subsequently been shown to be distributed in the brain [Uhl, G. R., et al., Proc. Natl. Acad. Sci. USA, **74**, 4059-4063 (1977), gastrointestinal tract [1). Kitabgi, P., Carraway, R. and Leeman, S. E., J. Biol. Chem., **251**, 7053 (1976); 2). Carraway, R., Kitabgi, P., and Leeman, S. E., J. Biol. Chem., **253**, 7996 (1978); 3). Helmstadler, V., Taugner, C., Feurle, G. E. and Frossman, W. G., Histochemistry, **53**, 35-41 (1977)] and pancreas [Feurle, G. E. and Niestroj, S., Pancreas, **6**, 202-207 (1991) and references cited therein] of various animals including human [Mai, J.

K., et al., Neuroscience, 22, 499-524 (1987)].

Although the physiological role of neurotensin has not yet been clearly understood, this endogenous peptide participates in a wide spectrum of central

5 [1). Prange, A. J. and Nemeroff, C. B., Annal. NY Acad. Sciences, 400, 368-375 (1982); 2). Stowe, Z. N. and Nemeroff, C. B., Life Sci., 49, 987-1002, (1991); 3) Kitabgi, P., Neurochem. Int., 14, 111-119 (1989); 4). Levant and Nemeroff, C. B., Current topics in Neuroendocrinology, 8, 231-262 (1988)] and
10 peripheral [Leeman, S. E., Aronin, N. and Ferris, C., Hormone Res., 38, 93-132 (1982)] biological functions.

Neurotensin is also known to release mast cell histamine, indicating that antagonists will be
15 useful in the treatment of allergic and inflammatory conditions, as well. [See, Rossei, S.S. and Miller, R.J., Life Sci., 31, 509-516 (1982) and Kurose, M. and Saeki, K., Eur. J. Pharmacol., 76, 129-136 (1981).]

20 Neurotensin, like most other peptides, is unable to cross the blood-brain barrier (BBB). However, certain peripheral effects of neurotensin have been observed after central administration of the peptide [Prange, A. J. and Nemeroff, C. B.,
25 Annal. NY Acad. Sciences, 400, 368-391 (1982). The direct application of neurotensin into the brain causes hypothermia, potentiation of barbiturate induced sedation, catalepsy, antinociception, blockade of psychostimulant-induced locomotor
30 activity and reduced food consumption. In the central nervous system (CNS), neurotensin behaves as a

neurotransmitter or neuromodulator [1) Uhl, G. R. and Snyder, S. H., Eur. J. Pharmacol., 41, 89-91 (1977); 2) Uhl, G. R., Annal. NY Acad. Sciences, 400, 132-149 (1982)], and has been shown to have close anatomical and biochemical associations with the dopaminergic (DA) system [Nemeroff, C. B., et al. Annal. NY Acad. Sciences, 400, 330-344 (1982)].

Neurotensin increases the synthesis and the turnover of DA in rat brain. Acute and chronic treatment with clinically efficacious antipsychotic drugs (e.g., haloperidol, chlorpromazine) have consistently demonstrated an increase in neurotensin concentrations in the nucleus accumbens and striatum while phenothiazines that are not antipsychotics did not produce this increase. Behaviorally, neurotensin, after central administration, mimics the effects of systemically administered neuroleptics. However, unlike classical neuroleptics (which primarily acts on D₂ receptors), neurotensin fails to bind to dopamine receptors or inhibit cAMP accumulation following DA receptor activation. Neurotensin does not block the stereotypy induced by DA agonists. The post-mortem studies of patients with schizophrenia showed an increase in the level of neurotensin in the Brodman's area 32 of human brain [Nemeroff, C. B., et. al., Science., 221, 972-975 (1983) and references cited therein], which suggest possible roles of neurotensin in the pathophysiology of this disease. Neurotensin receptors have also been implicated in Parkinson's disease and progressive supranuclear palsy [Chinaglia, G. et al., Neuroscience, 39, 351-360 (1990)].

Of the total body neurotensin in many mammalian species, more than 80% is present in the gastrointestinal tract, especially in the distal small intestine in the endocrine like N-cells. In the gut, neurotensin stimulates pancreatic secretion [Sakamoto, T., et al, Surgery, 96, 146-53 (1984)], inhibits gastric acid secretion and gastric emptying [Blackburn, A. M., Lancet, 1, 987-989 (1980)]. Neurotensin also stimulates the growth of small intestinal mucosa in an isolated defunctional loop of jejunum, which suggests a direct systemic effect of neurotensin in the gut. In addition, neurotensin can stimulate pancreatic exocrine secretion in mammals [Iwatsuki, K., et al., Clin. Expt. Pharmacol. Physiol., 18, 475-481 (1991) and references cited therein].

From the structural work, it is evident that the biological activity of neurotensin resides within the carboxy terminal five or six amino acid residues. The C-terminal hexapeptide NT⁸⁻¹³ has displayed full biological activity of the tridecapeptide. In contrast, all amino terminal partial sequences are essentially inactive [Leeman, S. E. and Carraway, R. E., Annal. NY Acad. Sciences, 400, 1-16 (1982)]. The C-terminal COOH group and two Arg residues are essential for the biological activity of NT⁸⁻¹³ as well as neurotensin. L-amino acids are required at positions-9,10,11 and 13, and only Arg⁸ can be replaced by D-Arg without loss of any activity. At the position-11, an aromatic amino acid is essential. Similarly, alkyl side-chains of Ile¹² and Leu¹³ are also necessary for full biological activity [Kitabgi,

P., Annal. NY Acad. Sciences, 400, 37-53 (1982)].

Most of the analogues of neurotensin examined generally behaved as agonists. However, two analogues D-Trp¹¹-NT and Tyr(Me)¹¹-NT have displayed partial antagonist activity [Rioux, F. R., et al., Eur. J. Pharmacol., 66, 373-379 (1980)].

5 The compounds useful in the novel method of treatment of this invention are known in the art having been published in European Patent Application EP 400,835 and EP 400,974 (Merck & Co., Inc.) where
10 they are alleged to be angiotensin II receptor antagonists useful in the treatment of hypertension and ocular hypertension. EP 400,835 disclosing benzimidazoles published on December 5, 1990, and EP
15 400,974 imidazo-6-fused heterocycles published on December 5, 1990.

 Although there are reports of peptidic neurotensin antagonists, they are rapidly degraded in vivo and not orally active and none are useful clinically. There are no reports of non-peptidic
20 neurotensin antagonists.

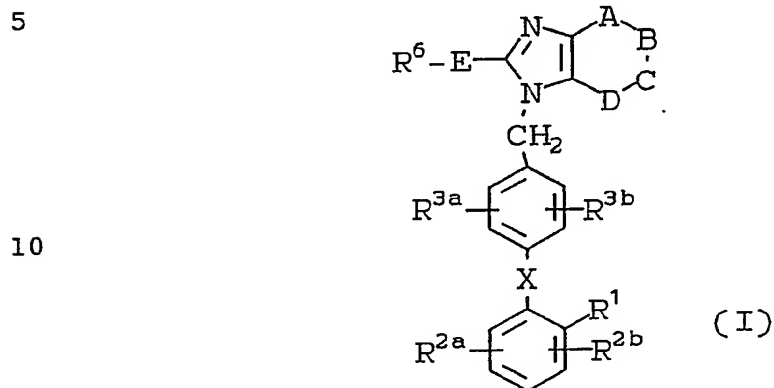
 Now with this invention there are provided non-peptidic neurotensin antagonists.

25

30

DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the novel method of treatment of this invention have structural formula I:



or a pharmaceutically acceptable salt thereof,
wherein:

R¹ is:

- (a) -NHSO₂R²³,
- (b) -NHSO₂NHCOR²³,
- (c) -NHCONHSO₂R²³,
- (d) -SO₂NHR²³,
- (e) -SO₂NHCOR²³,
- (f) -SO₂NHCONR⁹R²³,
- (g) -SO₂NHCOOR²³,
- (h) -SO₂NHOR²³,
- (i) -CH₂SO₂NHCOR²³,
- (j) -CH₂SO₂NHCONHR²³,
- (k) -CO₂H, or
- (l) -1H-tetrazol-5-yl;

R^{2a} and R^{2b} are independently H, Cl, Br, I, F, $-\text{NO}_2$,
 $-\text{NH}_2$, $\text{C}_1\text{-C}_4\text{-alkylamino}$, $\text{di}(\text{C}_1\text{-C}_4\text{ alkyl})\text{amino}$,
 $-\text{SO}_2\text{NHR}^9$, CF_3 , $\text{C}_1\text{-C}_4\text{-alkyl}$, or $\text{C}_1\text{-C}_4\text{-alkoxy}$;

R^{3a} is

- 5 (a) H,
 (b) Cl, Br, I, F,
 (c) $\text{C}_1\text{-C}_6\text{-alkyl}$,
 (d) $\text{C}_1\text{-C}_6\text{-alkoxy}$,
 (e) $\text{C}_1\text{-C}_6\text{-alkoxyalkyl}$;

10

R^{3b} is

- (a) H,
 (b) Cl, Br, I, F,
 (c) NO_2 ,
15 (d) $\text{C}_1\text{-C}_6\text{-alkyl}$,
 (e) $\text{C}_1\text{-C}_6\text{-acyloxy}$,
 (f) $\text{C}_1\text{-C}_6\text{-cycloalkyl}$
 (g) $\text{C}_1\text{-C}_6\text{-alkoxy}$,
 (h) $-\text{NHSO}_2\text{R}^4$,
20 (i) hydroxy $\text{C}_1\text{-C}_4\text{-alkyl}$,
 (j) aryl $\text{C}_1\text{-C}_4\text{-alkyl}$,
 (k) $\text{C}_1\text{-C}_4\text{-alkylthio}$,
 (l) $\text{C}_1\text{-C}_4\text{-alkyl sulfinyl}$,
 (m) $\text{C}_1\text{-C}_4\text{-alkyl sulfonyl}$,
25 (n) NH_2 ,
 (o) $\text{C}_1\text{-C}_4\text{-alkylamino}$,
 (p) $\text{C}_1\text{-C}_4\text{-dialkylamino}$,
 (q) fluoro $\text{C}_1\text{-C}_4\text{-alkyl}$,
 (r) $-\text{SO}_2\text{-NHR}^9$,

30

(s) aryl, or wherein aryl is phenyl or naphthyl optionally substituted with one or two substituents selected from the group consisting of Cl, Br, I, F, C₁-C₄-alkyl, C₁-C₄-alkoxy, NO₂, CF₃, C₁-C₄-alkylthio, OH, NH₂, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, CO₂H, and CO₂-C₁-C₄-alkyl;

(t) furyl;

R⁴ is H, C₁-C₆ alkyl, aryl or -CH₂-aryl;

R^{4a} is C₁-C₆-alkyl, aryl or -CH₂-aryl;

R⁵ is H, $\begin{array}{c} \text{R}^4 \\ | \\ \text{-CH-O-C-} \end{array} \begin{array}{c} \text{O} \\ || \\ \text{R}^{4a} \end{array}$;

E is a single bond, -NR¹³(CH₂)_s-, -S(O)_x-(CH₂)_s- where x is 0 to 2 and s is 0 to 5, -CH(OH)-, -O-, -CO-;

R⁶ is

(a) aryl unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of Cl, Br, I, F, -O-C₁-C₄-alkyl, C₁-C₄-alkyl, -NO₂, -CF₃, -SO₂NR⁹R¹⁰, -S-C₁-C₄-alkyl, -OH, -NH₂, C₃-C₇-cycloalkyl, C₃-C₁₀-alkenyl;

(b) C₁-C₉-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl each of which can be unsubstituted or substituted with a substituent selected from the group consisting of aryl, C₃-C₇-cycloalkyl, Cl, Br, I, F, -OH, -NH₂,

-NH(C₁-C₄-alkyl), -CF₂CF₃, -N(C₁-C₄-alkyl)₂,
-NH-SO₂R⁴, -COOR⁴, -CF₃, -CF₂CH₃, -SO₂NHR⁹; or

(c) an unsubstituted, monosubstituted or
disubstituted aromatic 5 or 6 membered
cyclic ring which can contain one or two
members selected from the group consisting of
N, O, S, and wherein the substituents are
members selected from the group consisting of
-OH, -SH, C₁-C₄-alkyl, C₁-C₄-alkyloxy, -CF₃,
Cl, Br, I, F, or NO₂,

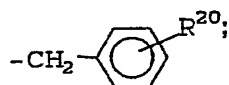
(d) perfluoro-C₁-C₄-alkyl,

(e) C₃-C₇-cycloalkyl optionally mono- or
disubstituted with C₁-C₄-alkyl or -CF₃;

R⁹ is H, C₁-C₅-alkyl, aryl or -CH₂-aryl;

R¹⁰ is H, C₁-C₄-alkyl;

R¹¹ is H, C₁-C₆-alkyl, C₂-C₄-alkenyl,
C₁-C₄-alkoxy-C₁-C₄-alkyl, or



R¹² is -CN, -NO₂ or -CO₂R⁴;

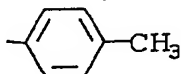
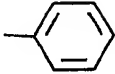
R¹³ is H, -CO(C₁-C₄-alkyl), C₁-C₆-alkyl, allyl,
C₃-C₆-cycloalkyl, phenyl or benzyl;

R¹⁴ is H, C₁-C₈-alkyl, C₁-C₈-perfluoroalkyl,
C₃-C₆-cycloalkyl, phenyl or benzyl;

R¹⁵ is H, C₁-C₆-alkyl;

R¹⁶ is H, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, phenyl or benzyl;

5 R¹⁷ is -NR⁹R¹⁰, -OR¹⁰, -NHCONH₂, -NHCSNH₂,

10 -NHSO₂ -  or -NHSO₂ -  ;

R¹⁸ and R¹⁹ are independently C₁-C₄-alkyl or taken together are -(CH₂)_q-where q is 2 or 3;

15 R²⁰ is H, -NO₂, -NH₂, -OH or -OCH₃;

R²² is

- 20 (a) phenyl, unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of: Cl, Br, I, or F, -O-C₁-C₄-alkyl, C₁-C₄-alkyl, -NO₂, -CF₃, -SO₂NR⁹R¹⁰, -S-C₁-C₄-alkyl, -OH, -NH₂, -COOR⁴, C₃-C₇-cycloalkyl, and C₃-C₁₀-alkenyl;
- 25 (b) C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl each of which is unsubstituted or substituted with one or more substituents selected from the group consisting of aryl, C₃-C₇-cycloalkyl, Cl, Br, I, F, -OH, -O-C₁-C₄-alkyl, -NH₂, -NH(C₁-C₄-alkyl), -N(C₁-C₄-alkyl)₂, -NH-SO₂R⁴, -COOR⁴, -SO₂NHR⁹, and -S-C₁-C₄-alkyl;
- 30

- (c) an unsubstituted, monosubstituted or disubstituted aromatic 5 or 6 membered ring comprising one or two heteroatoms selected from the group consisting of N, O, and S, and wherein the substituents are members selected from the group consisting of: -OH, -SH, C₁-C₄-alkyl, C₁-C₄-alkyloxy, -CF₃, -COOR⁴, Cl, Br, I, F, and NO₂; or
- (d) C₃-C₇-cycloalkyl unsubstituted or substituted with one or more substituents selected from the group consisting of: C₁-C₄-alkyl, -O-C₁-C₄-alkyl, -S-C₁-C₄-alkyl, -OH, -COOR⁴, C₁-C₄-perfluoroalkyl, Cl, Br, F, and I, or
- (e) (C₁-C₄)-perfluoroalkyl;

R²³ is

- (a) aryl,
- (b) heteroaryl wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted five- or six-membered aromatic ring which can optionally contain 1 to 3 heteroatoms selected from the group consisting of O, N or S and wherein the substituents are members selected from the group consisting of -OH, -SH, -C₁-C₄-alkyl, -C₁-C₄-alkoxy, halo(Cl, Br, F, I), -NO₂, -CO₂H, -CO₂-C₁-C₄-alkyl, -NH₂, -NH(C₁-C₄-alkyl) and -N(C₁-C₄-alkyl)₂;
- (c) C₃-C₄-cycloalkyl,

- (d) C₁-C₈-alkyl which can be unsubstituted or substituted with one or two substituents selected from the group consisting of: aryl heteroaryl, -OH, -SH, -C₁-C₄-alkyl, -O(C₁-C₄-alkyl),
 5 -S(C₁-C₄-alkyl), -C₃-C₈-cycloalkyl, -CF₃, Cl, Br, F, I, -NO₂, -CO₂H, -CO₂-C₁-C₄-alkyl, -CONR⁴R²², -OCONR⁴R²², -NH₂, -NH(C₁-C₄-alkyl), -NHCOR^{4a}, NR⁴COOR⁹,
 10 -N(C₁-C₄-alkyl)₂, -NR⁴COR²², -NR⁴SO₂R²², -SO₂NR⁴R²², -PO₃H, -PO(OH)(C₁-C₄-alkyl), -PO(OH)(aryl), or -PO(OH)(O-C₁-C₄-alkyl),
 (e) perfluoro-C₁-C₄-alkyl;

X is absent or is

- 15 (a) a carbon-carbon single bond,
 (b) -CO-,
 (c) -O-,
 (d) -S-,
 20 (e) -N-,
 |
 R¹³
 (f) -CON-,
 |
 R¹⁵
 (g) -NCO-,
 |
 R¹⁵
 25 (h) -OCH₂-,
 (i) -CH₂O-
 (j) -SCH₂-,
 (k) -CH₂S-,
 (l) -NHC(R⁹)(R¹⁰),
 30 (m) -NR⁹SO₂-,
 (n) -SO₂NR⁹-,

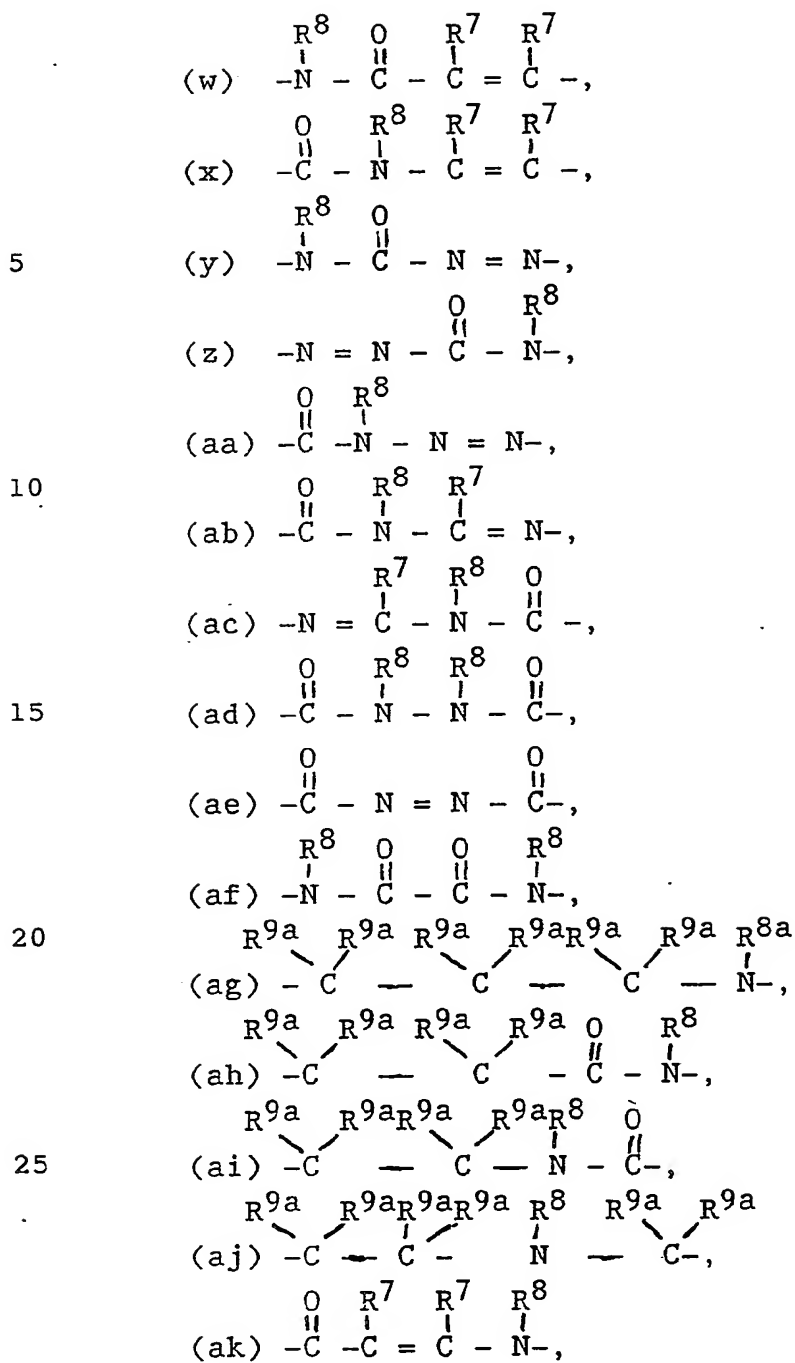
- (o) $-C(R^9)(R^{10})NH-$,
 (p) $-CH=CH-$,
 (q) $-CF=CF-$,
 (r) $-CH=CF-$,
 (s) $-CF=CH-$,
 5 (t) $-CH_2CH_2-$,
 (u) $-CF_2CF_2-$,
 (v) $-CH-\overset{CH_2}{CH}-$ and $C \overset{CH_2}{CH_2}$,
 10 CH_2 ,

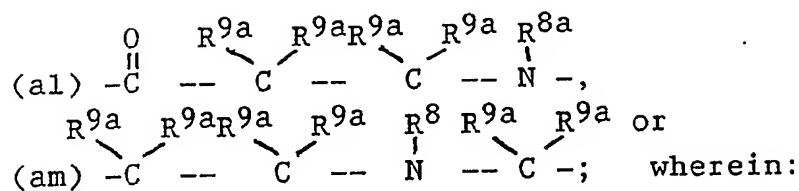
Z is O, NR^{13} or S;

15 -A-B-C-D- represents the constituent atoms of a 6-member carbocycle or a 6-member saturated or unsaturated heterocyclic ring with the imidazole to which they are attached containing 1 to 3 nitrogen atoms and includes the following:

- 20 (a) $\begin{array}{cccc} R^7 & R^7 & R^7 & R^7 \\ | & | & | & | \\ -C & = & C & - C = C- \end{array}$,
 (b) $\begin{array}{cccc} R^7 & R^7 & R^7 & \\ | & | & | & \\ -C & = & C & - C = N- \end{array}$,
 25 (c) $\begin{array}{cccc} & R^7 & R^7 & R^7 \\ & | & | & | \\ -N & = & C & - C = C- \end{array}$,
 (d) $\begin{array}{cccc} R^7 & R^7 & & R^7 \\ | & | & & | \\ -C & = & C & - N = C- \end{array}$,
 (e) $\begin{array}{cccc} R^7 & & R^7 & R^7 \\ | & & | & | \\ -C & = & N & - C = C- \end{array}$,
 30 (f) $\begin{array}{cccc} R^7 & R^7 & & \\ | & | & & \\ -C & = & C & - N = N- \end{array}$,

- (g)
$$\begin{array}{c} \text{R}^7 \quad \text{R}^7 \\ | \quad | \\ -\text{N} = \text{N} - \text{C} = \text{C}-, \end{array}$$
- (h)
$$\begin{array}{c} \text{R}^7 \quad \text{R}^7 \\ | \quad | \\ -\text{C} = \text{N} - \text{N} = \text{C}-, \end{array}$$
- 5 (i)
$$\begin{array}{c} \text{R}^7 \quad \text{R}^7 \\ | \quad | \\ -\text{N} = \text{C} - \text{C} = \text{N}-, \end{array}$$
- (j)
$$\begin{array}{c} \text{R}^7 \quad \text{R}^7 \\ | \quad | \\ -\text{N} = \text{C} - \text{N} = \text{C}-, \end{array}$$
- (k)
$$\begin{array}{c} \text{R}^7 \quad \text{R}^7 \\ | \quad | \\ -\text{C} = \text{N} - \text{C} = \text{N}-, \end{array}$$
- 10 (l)
$$\begin{array}{c} \text{R}^7 \\ | \\ -\text{N} = \text{N} - \text{N} = \text{C}-, \end{array}$$
- (m)
$$\begin{array}{c} \text{R}^7 \\ | \\ -\text{C} = \text{N} - \text{N} = \text{N}-, \end{array}$$
- 15 (n)
$$\begin{array}{c} \text{R}^7 \\ | \\ -\text{N} = \text{N} - \text{C} = \text{N}-, \end{array}$$
- (o)
$$\begin{array}{c} \text{R}^7 \\ | \\ -\text{N} = \text{C} - \text{N} = \text{N}-, \end{array}$$
- (p)
$$\begin{array}{c} \text{O} \quad \text{R}^8 \quad \text{O} \quad \text{R}^8 \\ || \quad | \quad || \quad | \\ -\text{C} - \text{N} - \text{C} - \text{N}-, \end{array}$$
- 20 (q)
$$\begin{array}{c} \text{R}^8 \quad \text{O} \quad \text{R}^8 \quad \text{O} \\ / \quad || \quad / \quad || \\ -\text{N} - \text{C} - \text{N} - \text{C}-, \end{array}$$
- (r)
$$\begin{array}{c} \text{R}^7 \quad \text{R}^7 \quad \text{O} \quad \text{R}^8 \\ | \quad | \quad || \quad | \\ -\text{C} = \text{C} - \text{C} - \text{N}-, \end{array}$$
- (s)
$$\begin{array}{c} \text{R}^8 \quad \text{O} \quad \text{R}^7 \\ | \quad || \quad | \\ -\text{N} - \text{C} - \text{C} = \text{N}-, \end{array}$$
- 25 (t)
$$\begin{array}{c} \text{R}^7 \quad \text{O} \quad \text{R}^8 \\ | \quad || \quad | \\ -\text{N} = \text{C} - \text{C} - \text{N}-, \end{array}$$
- (u)
$$\begin{array}{c} \text{R}^7 \quad \text{R}^7 \quad \text{O} \quad \text{R}^8 \\ | \quad | \quad || \quad | \\ -\text{C} = \text{C} - \text{C} - \text{N}-, \end{array}$$
- 30 (v)
$$\begin{array}{c} \text{R}^7 \quad \text{R}^7 \quad \text{R}^8 \quad \text{O} \\ | \quad | \quad | \quad || \\ -\text{C} = \text{C} - \text{N} - \text{C}-, \end{array}$$

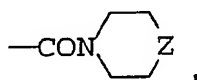




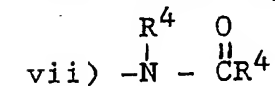
5 R^7 groups can be the same or different and represent:

- a) hydrogen,
 b) C_1-C_6 straight or branched chain alkyl, or
 10 C_2-C_6 alkenyl, or alkynyl each of which is unsubstituted or substituted with:

- i) $-OH$
 ii) C_1-C_4 -alkoxy,
 iii) $-CO_2R^4$,
 iv) $-OCOR^4$,
 15 v)



- 20 vi) $-CON(R^4)_2$



- viii) $-N(R^4)_2$,

- ix) aryl as defined above,
 x) heterocyclic as defined in (p) below,

- 25 xi) $-S(O)_x R^{23}$,

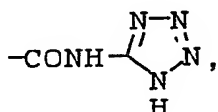
- xii) tetrazol-5-yl,

- xiii) $-CONHSO_2 R^{23}$,

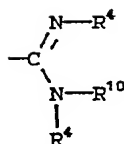
- xiv) $-SO_2NH$ -heteroaryl,

- 30 xv) $-SO_2NHCOR^{23}$,

- xvi)

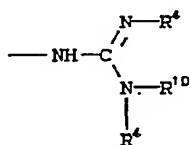


xvii)



5

xviii)



10

xix) $-\text{PO}(\text{OR}^4)_2$,

xx) $-\text{PO}(\text{OR}^4)\text{R}^9$,

15

c) Cl, Br, I, F,

d) perfluoro- $\text{C}_1\text{-C}_4$ -alkyl,

e) $-\text{OH}$,

f) $-\text{NH}_2$,

g) $-\text{N}-\text{R}^{23}$,
 $|$
 R^4

20

h) $-\text{N}-\text{COR}^{23}$,
 $|$
 R^4

i) $-\text{OR}^{23}$,

j) $-\text{CO}_2\text{R}^4$,

25

k) $-\text{CON}(\text{R}^4)_2$,

l) $-\text{NH}-\text{C}_3\text{-C}_7\text{-cycloalkyl}$,

m) $\text{C}_3\text{-C}_7\text{-cycloalkyl}$,

n) aryl as defined above, or

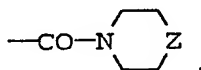
o) heterocyclic which is a five- or six-
 membered saturated or unsaturated ring

30

containing up to three heteroatoms selected

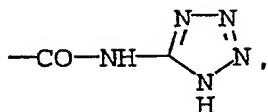
from the group consisting of O, N or S
wherein S may in the form of sulfoxide or
sulfone and which may be optionally
substituted with one or two substituents
which are members selected from the group
consisting of Cl, Br, F, I, C₁-C₄-alkyl,
C₁-C₄-alkoxy, C₁-C₄-S(O)_x- where x is as
defined above, CF₃, NO₂, OH, CO₂H,
CO₂-C₁-C₄-alkyl, or -N(R⁴)₂;

- p) -CN,
- q) (CH₂)_nN- wherein n is 4 to 6,
- r) -SO₂N(R⁴)₂;
- s) tetrazol-5-yl,
- t) -CONHSO₂R²³,
- u) -PO(OR⁴)₂,
- v) -NHSO₂CF₃,
- w) -SO₂NH-heteroaryl,
- x) -SO₂NHCOR²³,
- y) -S(O)_x-R²³,
- z)

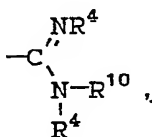


- aa) -PO(OR⁴)R⁹,
- bb) -NHSO₂R²³,
- cc) -NHSO₂NHR²³,
- dd) -NHSO₂NHCOR²³,
- ee) -NHCONHSO₂R²³,
- ff) -N(R⁴)CO₂R²³,

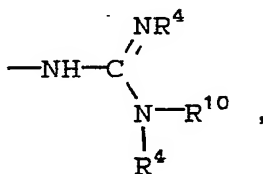
- $R^4 \quad R^4$
 gg) $-N-CON-R^{23}$,
 hh) $-CO-aryl$,
 ii)



- jj) $-CO-C_1-C_4-alkyl$,
 kk) $-SO_2NH-CN$,
 ll)



mm)



20 R^8 groups can be the same or different and represent:

- a) hydrogen,
 b) $C_1-C_6-alkyl$ or $alkenyl$ either unsubstituted
 25 or substituted with hydroxy, $C_1-C_4-alkoxy$,
 $-N(R^4)_2$, $-CO_2R^4$, or $C_3-C_5-cycloalkyl$;
 c) $C_3-C_5-cycloalkyl$,

30 R^{8a} is R^8 or C_1-C_4-acyl ; and

R^{9a} groups can be the same or different and represent:

- a) hydrogen,
- b) C₁-C₆-alkyl either unsubstituted or substituted with
 - i) hydroxy,
 - ii) -CO₂R⁴,
 - iii) -CONHR⁴, or
 - iv) -CON(R⁴)₂.

10

The terms "alkyl", "alkenyl", "alkynyl" and the like include both the straight chain and branched chain species of these generic terms wherein the number of carbon atoms in the species permit. Unless otherwise noted, the specific names for these generic terms shall mean the straight chain species. For example, the term "butyl" shall mean the normal butyl substituent, n-butyl.

20

One embodiment of the novel compounds of this invention is the class compounds of Formula I wherein:

R¹ is:

- 25 (a) -NHSO₂R²³,
- (b) -NHSO₂NHCOR²³,
- (c) -NHCONHSO₂R²³,
- (d) -SO₂NHR²³,
- (e) -SO₂NHCOR²³,
- 30 (f) -SO₂NHCONR⁹R²³,
- (g) -SO₂NHCOOR²³,

- (h) $-\text{SO}_2\text{NHR}^{23}$,
- (i) $-\text{CH}_2\text{SO}_2\text{NHCOR}^{23}$,
- (j) $-\text{CH}_2\text{SO}_2\text{NHCONHR}^{23}$, or
- (k) $-\text{1H-tetrazol-5-yl}$;

5 X is a single bond;

R^{2a} and R^{2b} are independently:

- a) $\text{C}_1\text{-C}_4\text{-alkyl}$,
- b) Cl , Br , I , F ,
- 10 c) hydrogen;

R^{3a} and R^{3b} are independently:

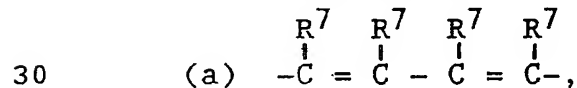
- a) $\text{C}_1\text{-C}_6\text{-alkyl}$,
- b) Cl , Br , I , F , or
- 15 c) $\text{C}_1\text{-C}_6\text{-alkoxy}$,
- d) hydrogen;

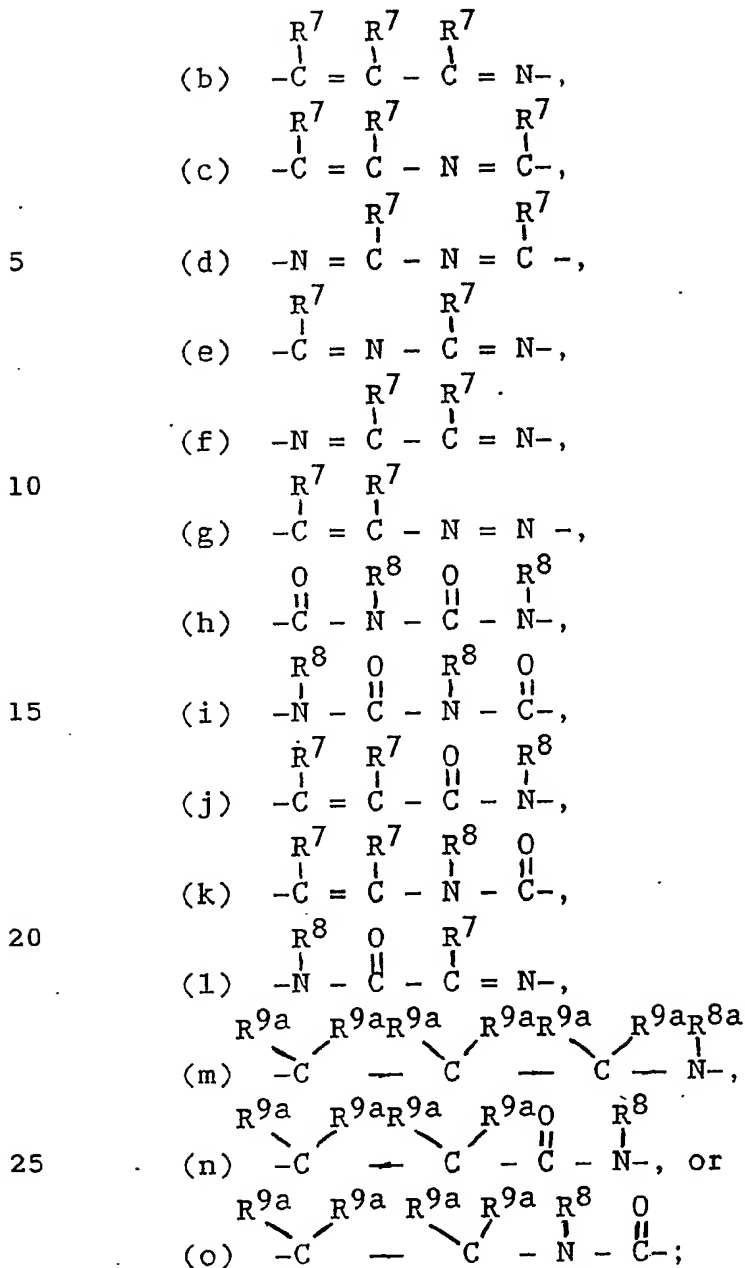
R^4 is H , or $\text{C}_1\text{-C}_4\text{-alkyl}$;

20 E is a single bond or $-\text{S}-$;

R^6 is a branched or straight chain $\text{C}_1\text{-C}_6\text{-alkyl}$,
 $\text{C}_3\text{-C}_7\text{-cycloalkyl}$, $\text{C}_2\text{-C}_6\text{-alkenyl}$ or $\text{C}_2\text{-C}_6\text{-alkynyl}$
each of which is either unsubstituted or
25 substituted with $\text{C}_1\text{-C}_4\text{-alkylthio}$, $\text{C}_1\text{-C}_4\text{-alkoxy}$,
 CF_3 , CF_2CF_3 or $-\text{CF}_2\text{CH}_3$;

A-B-C-D- represents:





R^7 groups are the same or different and represent:

- a) hydrogen,
- b) $-C_1-C_4$ -alkyl, either unsubstituted or substituted with:

- i) -OH,
- ii) $-\text{CO}_2\text{R}^4$,
- iii) $-\text{NH}_2$,
- iv) $(\text{C}_1\text{-C}_4 \text{ alkyl})\text{amino}$,
- v) $\text{di}(\text{C}_1\text{-C}_4\text{-alkyl})\text{amino}$,
- 5 c) Cl, Br, F, I,
- d) $-\text{CF}_3$,
- e) -OH,
- f) $-\text{N}(\text{R}^4)_2$,
- g) $-\text{C}_1\text{-C}_4\text{-alkoxy}$,
- 10 h) $-\text{CO}_2\text{R}^4$,
- i) $-\text{CONH}_2$,
- j) $-\text{C}_3\text{-C}_7\text{-cycloalkyl}$,
- k) aryl,
- l) heterocyclic as defined above,
- 15 m) $-\text{CF}_3$,
- n) tetrazol-5-yl,
- o) $-\text{CONHSO}_2\text{R}^{23}$;

R^8 groups are the same or different and represent,

- 20 a) hydrogen,
- b) $\text{C}_1\text{-C}_4\text{-alkyl}$ either unsubstituted or substituted with -OH or $-\text{CO}_2\text{R}^4$; and

R^{8a} represents

- 25 a) hydrogen,
- b) $\text{C}_1\text{-C}_4 \text{ alkyl}$, or
- c) $(\text{C}_1\text{-C}_4\text{-alkyl})\text{CO-}$; and

R^{9a} groups are the same or different and represent:

- 30 a) hydrogen,
- b) $\text{C}_1\text{-C}_4\text{-alkyl}$.

Another embodiment of this invention is the group of compounds of Formula I wherein:

R¹ is:

- (a) -SO₂NHCOR²³,
- 5 (b) -SO₂NHCONR⁹R²³,
- (c) -SO₂NHCOOR²³,
- (d) -SO₂NHOR²³,
- (e) -CH₂SO₂NHCOR²³, or
- (f) -1H-tetrazol-5-yl;

10

R^{2a} and R^{2b} are independently:

- a) C₁-C₄-alkyl, or
- b) chloro,
- c) hydrogen;

15

R^{3a} and R^{3b} are independently:

- a) C₁-C₄-alkyl,
- b) chloro, or
- c) C₁-C₄-alkoxy,
- 20 d) hydrogen;

20

E is a single bond or -S-;

R⁶ is

- 25 (a) a branched or straight chain C₁-C₆-alkyl; C₂-C₆-alkenyl or C₂-C₆-alkynyl each of which is either unsubstituted or substituted with C₁-C₄-alkylthio, C₁-C₄-alkoxy, CF₃, CF₂CF₃ or -CF₂CH₃;
- 30 (b) C₃-C₇-cycloalkyl;
- (c) perfluoro-C₁-C₄-alkyl;

A-B-C-D- represents:

- (a) $\begin{array}{cccc} R^7 & R^7 & R^7 & R^7 \\ | & | & | & | \\ -C & = C & - C & = C-, \end{array}$
- (b) $\begin{array}{cccc} R^7 & R^7 & R^7 & \\ | & | & | & \\ -C & = C & - C & = N-, \end{array}$
- (c) $\begin{array}{cccc} R^7 & R^7 & & R^7 \\ | & | & & | \\ -C & = C & - N & = C-, \end{array}$
- (d) $\begin{array}{cccc} & R^7 & & R^7 \\ & | & & | \\ -N & = C & - N & = C-, \end{array}$
- (e) $\begin{array}{cccc} R^7 & & R^7 & \\ | & & | & \\ -C & = N & - C & = N-, \end{array}$
- (f) $\begin{array}{cccc} & R^7 & R^7 & \\ & | & | & \\ -N & = C & - C & = N-, \end{array}$
- (g) $\begin{array}{cccc} & & R^7 & R^7 \\ & & | & | \\ -N & = N & - C & = C-, \end{array}$
- (h) $\begin{array}{cccc} O & R^8 & O & R^8 \\ || & | & || & | \\ -C & - N & - C & - N-, \end{array}$
- (i) $\begin{array}{cccc} R^8 & O & R^8 & O \\ | & || & | & || \\ -N & - C & - N & - C-, \end{array}$
- (j) $\begin{array}{cccc} R^7 & R^7 & O & R^8 \\ | & | & || & | \\ -C & = C & - C & - N-, \end{array}$
- (k) $\begin{array}{cccc} R^8 & O & R^7 & \\ | & || & | & \\ -N & - C & - C & = N-, \end{array}$
- (l) $\begin{array}{cccc} & R^7 & R^8 & O \\ & | & | & || \\ -N & - C & - N & - C, \text{ or } \end{array}$
- (m) $\begin{array}{cccc} R^7 & R^7 & R^8 & O \\ | & | & | & || \\ -C & = C & - N & - C-; \end{array}$

R^7 groups are the same or different and represent:

- a) hydrogen,
- b) $-C_1-C_4$ -alkyl, either unsubstituted or substituted with $-OH$ or $-CO_2R^4$;

- c) Cl, Br, F, I,
- d) -OH,
- e) -N(R⁴)₂,
- f) -C₁-C₄-alkoxy, or
- g) -CO₂R⁴,
- 5 h) aryl,
- i) heterocyclic as defined above,
- j) -CF₃,
- k) tetrazol-5-yl,

10 R⁸ groups are the same or different and represent:

- a) H,
- b) C₁-C₄-alkyl either unsubstituted or substituted with -OH or -CO₂R⁴.

15 In a class of this embodiment are those compounds of Formula I wherein:

R¹ is:

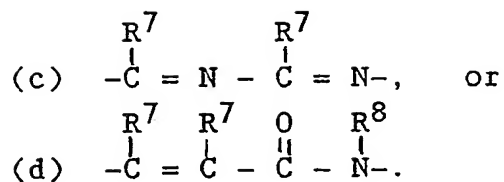
- (a) -SO₂NHCOR²³,
- 20 (b) -SO₂NHCONR⁹R²³,
- (c) -SO₂NHCOOR²³,
- (d) -SO₂NHOR²³,
- (e) -CH₂SO₂NHCOR²³, or
- (f) -1H-tetrazol-5-yl;

25

E is a single bond; and

A-B-C-D represents:

- 30 (a) $\begin{array}{cccc} R^7 & R^7 & R^7 & R^7 \\ | & | & | & | \\ -C & = & C & - C = C-, \end{array}$
- (b) $\begin{array}{cccc} R^7 & R^7 & R^7 & \\ | & | & | & \\ -C & = & C & - C = N-, \end{array}$



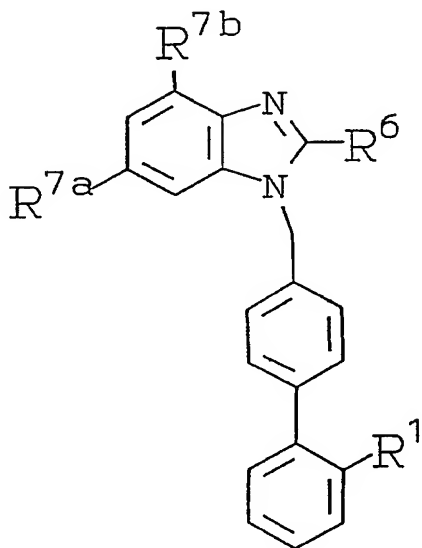
5 Exemplifying this class are the compounds shown in
Tables I and II

TABLE I

10

15

20



25

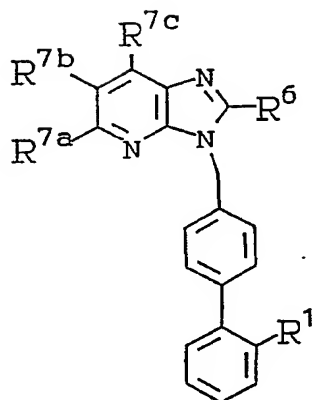
30

	<u>R¹</u>	<u>R⁶</u>	<u>R^{7a}</u>	<u>R^{7b}</u>
	SO ₂ NHCO-Ph	ethyl	methyl	methyl
	SO ₂ NHCO-4-pyridyl	ethyl	methyl	methyl
	SO ₂ NHCO-propyl	ethyl	methyl	methyl
	SO ₂ NHCO-n-heptyl	ethyl	methyl	methyl
	SO ₂ NHCOCH ₂ CH ₂ -cyclopentyl	ethyl	methyl	methyl
	SO ₂ NHCO-(3-aminophenyl)	ethyl	methyl	methyl

	<u>R¹</u>	<u>R⁶</u>	<u>R^{7a}</u>	<u>R^{7b}</u>
	SO ₂ NHCOCH ₂ NHBoc	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₅ NH ₂	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₅ NHBoc	ethyl	methyl	methyl
5	SO ₂ NHCOCH ₂ NH ₂	ethyl	methyl	methyl
	SO ₂ NHCO-(4-methoxyphenyl)	ethyl	methyl	methyl
	SO ₂ NHCO-cyclopropyl	ethyl	CO ₂ Me	methyl
	SO ₂ NHCO-(4-aminophenyl)	ethyl	CO ₂ Me	methyl
	SO ₂ NHCOCH ₂ CH ₂ CO-N-	ethyl	methyl	methyl
10	morpholinyl			
	SO ₂ NHCO-2-thienyl	ethyl	CO ₂ Me	methyl
	SO ₂ NHCO(CH ₂) ₅ NHBoc	ethyl	CO ₂ Me	methyl
	SO ₂ NHPO(OCH ₂ Ph) ₂	ethyl	methyl	methyl
	SO ₂ NHCOCF ₂ Cl	ethyl	methyl	methyl
15	SO ₂ NHSO ₂ -N-methyl-N-	ethyl	methyl	methyl
	piperidinyl			
	SO ₂ NHCO ₂ CH ₂ CH ₃	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₃ NH ₂	ethyl	methyl	methyl
	SO ₂ NHCO-3-aminophenyl	ethyl	CO ₂ Me	methyl
20	SO ₂ NHCO-4-dimethylamino	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₅ NHBoc	cyclopropyl	methyl	methyl
	SO ₂ NHCO-4-tolyl	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₄ CO ₂ Et	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₄ CO ₂ H	ethyl	methyl	methyl
25	SO ₂ NHCO-phenyl	cyclopropyl	methyl	methyl
	SO ₂ NHCO-N-morpholinyl	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₅ N(CH ₃) ₂	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₅ NH ₂	ethyl	methyl	methyl
	SO ₂ NHCO-4-(N-t-butoxy-	ethyl	methyl	methyl
30	carbonylpiperidinyl)			
	SO ₂ NHCO(CH ₂) ₂ CH(NHBoc)-	ethyl	methyl	methyl
	(CO ₂ t-Bu)			
	SO ₂ NHCO(CH ₂) ₆ NH ₂	ethyl	methyl	methyl

	<u>R¹</u>	<u>R⁶</u>	<u>R^{7a}</u>	<u>R^{7b}</u>
	SO ₂ NHCO-cyclopropyl	ethyl	CH ₂ OH	methyl
	SO ₂ NHCO-2-thiazolyl	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₃ NHt-Boc	ethyl	methyl	methyl
5	SO ₂ NHCO(CH ₂) ₃ NHt-Boc	ethyl	methyl	methyl
	SO ₂ NHCO-cyclopropyl	ethyl	CON(CH ₃) ₂	methyl

Table II



	<u>R¹</u>	<u>R⁶</u>	<u>R^{7a}</u>	<u>R^{7b}</u>	<u>R^{7c}</u>
	SO ₂ NHCOphenyl	ethyl	methyl	bromine	methyl
25	tetrazol-5-yl	butyl	methyl	N(benzyl)CObutyl	H
	tetrazol-5-yl	butyl	methyl	NHCON(phenyl) ₂	H

The compounds of Formula (I) can be synthesized using the reactions and techniques described in published European Patent Applications EP 400,835 and EP 400,974 (Merck & Co.). The above mentioned applications disclose the compounds of this

invention where they are alleged to be angiotensin II receptor antagonists useful in the treatment of hypertension and ocular hypertension.

The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the functionality present on the heterocycle and in the reactants being employed should be consistent with the chemical transformations being conducted. Depending upon the reactions and techniques employed, optimal yields may require changing the order of synthetic steps or use of protecting groups followed by deprotection.

The compounds useful in the novel method treatment of this invention form salts with various inorganic and organic acids and bases which are also within the scope of the invention. Such salts include ammonium salts, alkali metal salts like sodium and potassium salts, alkaline earth metal salts like the calcium and magnesium salts, salts with organic bases; e.g., dicyclohexylamine salts, N-methyl-D-glucamine, salts with amino acids like arginine, lysine, and the like. Also, salts with organic and inorganic acids may be prepared; e.g., HCl, HBr, H₂SO₄, H₃PO₄, methanesulfonic, toluenesulfonic, maleic, fumaric, camphorsulfonic.

The salts can be formed by conventional means, such as by reacting the free acid or free base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such

as water which is then removed in vacuo or by freeze-drying or by exchanging the cations of an existing salt for another cation on a suitable ion exchange resin.

5 Neurotensin is a peptide hormone and the assays described below have been developed to identify neurotensin antagonists and to determine their efficacy in vitro. The following two assays have been employed for that purpose.

10

RAT FOREBRAIN RECEPTOR ASSAY

Male rats are sacrificed by decapitation following ether anesthetization. Forebrains are
15 homogenized using a polytron in 20 volumes 50 mM Tris HCl, pH 7.4, and centrifuged at 50,000 x g for 20 min. The final pellet is washed twice by rehomogenization and centrifugation as before. The
20 final pellet is resuspended at a concentration of 8 mg tissue (wet weight) per 0.750 ml of 50 μ M Tris HCl, pH 7.4, which also contains 1 mM EDTA, 4 μ g/ml bacitracin, 5 μ M levocabastine HCl, 1mM phenanthroline, 10 μ g/ml soybean trypsin inhibitor and 100 μ M phenyl methyl sulfonyl fluoride. Assay
25 tubes (13 X 100 polypropylene) receive 1) 100 μ l buffer or 10 μ M neurotensin (for non-specific binding) 2) 100 μ l of 60 pM [125 I]neurotensin 3) 20 μ l test compounds 4) 750 μ l tissue suspension and 5) enough buffer to bring final volume to 1 ml. After
30 30 minutes at room temp, the samples are filtered using a Brandel M24 cell harvester with GF/B

filtermats that have been presoaked in 0.2% polyethyleneimine for 2 hours. The tubes are rinsed with 3 X 4 ml of ice cold 10 mM Tris buffer (pH 7.4 at room temperature). The filter discs are placed in 12 X 75 mM polypropylene tubes for counting on as
5 Packard Multi-Prias gamma counter.

HUMAN HT-29 CELL MEMBRANE ASSAY

HT-29 cells were routinely grown in 225 cm² Costar tissue culture flasks at 37°C in a humidified atmosphere of 5% CO₂/95% air in Dulbecco's modified Eagle's medium with high glucose containing 50 U/ml penicillin, 50 µg/ml streptomycin, 5% fetal bovine serum and 5% newborn calf serum. Cells were
10 subcultured with 0.25% trypsin at a ratio of 1:6 with confluence being reached at 48 to 72 hrs. Cells from confluent flasks (approx. 1×10^8 cells/flask) were harvested by scraping. The cells were pelleted by centrifugation (1000 x g, 5 min), resuspended in 50
15 mM Tris HCl, pH 7.4, and homogenized with a polytron (setting 7 for 10 sec.). Cell membranes were washed twice by centrifugation (50,000 x g, 15 min) and rehomogenization. The resulting pellet was either
20 frozen at -70°C for future use or run directly in the assay by resuspending at a concentration of 0.5×10^6 cells per 0.750 ml of assay buffer (50 mM Tris HCl, pH 7.4, containing 1 mM EDTA, 40 µg/ml bacitracin, 1 mM phenanthroline, 10 µg/ml soybean trypsin inhibitor and 100 µM phenylmethylsulfonyl fluoride).
25
30

Assay tubes (13 x 100 polypropylene) receive 1) 100 μ l buffer or 10 μ M neurotensin (for non-specific binding) 2) 100 μ l of 60 pM [125 I]neurotensin 3) 20 μ l test compounds 4) 750 μ l cell membrane suspension and 5) enough buffer to bring final volume to 1 ml. After 30 minutes at room temperature, the samples are filtered using a Brandel M24 cell harvester with GF/B filtermats that have been presoaked in 0.2% polyethyleneimine for 2 hours. The tubes are rinsed with 3 x 4 ml of ice cold 10 mM Tris buffer (pH 7.4 at room temperature). The filter discs are placed in 12 x 75 mM polypropylene tubes for counting on as Packard Multi-Prias gamma counter. [The above assay is derived from the assay described in Kitabgi, P. *et al.*, Molecular Pharmacology, 18, 11-19 (1980)].

NEUROTENSIN BINDING ASSAY USING HUMAN FRONTAL CORTEX

Post-mortem human brain is obtained through the National Disease Research Interchange (Philadelphia, PA). The donors were without psychiatric or neurological abnormalities. Frontal cortex is dissected free of white matter and homogenized using a polytron in 20 volumes 50 mM Tris HCl, pH 7.4, and centrifuged at 50,000 x g for 20 min. The resulting pellet is washed twice by rehomogenization and centrifugation as before. The final pellet is resuspended at a concentration of 8 mg tissue (wet weight) per 0.750 ml of 50 mM Tris HCl, pH 7.4, which also contains 1 mM EDTA, 4 μ g/ml bacitracin, 1 mM phenanthroline, 10 μ g/ml soybean trypsin inhibitor and 100 μ M phenyl methyl sulfonyl

fluoride. Assay tubes (13 x 100 polypropylene) receive 1) 100 μ l buffer or 10 μ M neurotensin (for non-specific binding) 2) 100 μ l of 60 pM [125 I]neurotensin 3) 20 μ l test compounds 4) 750 μ l tissue suspension and 5) enough buffer to bring final
5 volume to 1 ml. After 30 minutes at room temp, the samples are filtered using a Brandel M24 cell harvester with GF/B filtermats that have been presoaked in 0.2% polyethyleneimine for 2 hours. The tubes are rinsed with 3 x 4 ml of ice cold 10mM Tris
10 buffer (pH 7.4 at room temperature). The filter discs are placed in 12 x 75 mM polypropylene tubes for counting on a Packard Multu-Prias gamma counter.

Using the methodology described above, representative compounds of the invention were
15 evaluated and all were found to exhibit an activity of at least $IC_{50} < 50 \mu$ M thereby demonstrating and confirming the utility of the compounds of the invention as effective neurotensin antagonists.

Typically, these combinations can be
20 formulated into pharmaceutical compositions as discussed below.

About 1 to 100 mg. of compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable
25 vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the
30 range indicated is obtained.

Illustrative of the adjuvants which can be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent
5 such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the unit dosage
10 unitform is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated
15 with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be
20 formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a
25 synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The following examples further illustrate the preparation of the compounds of Formula I and
30 their incorporation into pharmaceutical compositions

and, as such, are not to be considered or construed as limiting the invention recited in the appended claims.

5 2-Butyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-
3H-imidazo[4,5-b]pyridine (Example 7)

2-propyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-
3H-imidazo[4,5-b]pyridine (Example 8)

10 Methyl-2-propyl-3-(2'-(tetrazol-5-yl)biphenyl-4-
yl)methyl-7-3H-imidazo[4,5-b]pyridine (Example 9)

2-butyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-
methyl-3H-imidazo[4,5-b]pyridine (Example 10)

15 8-Butyl-1,3-dimethyl-7-(2'-(tetrazol-5-yl)biphen-4-yl)
methyl-1,2,3,6-tetrahydro-2,6-dioxopurine (Example 11)

6-Chloro-8-propyl-9-(2'-tetrazol-5-yl)biphen-4-yl)-
20 methylpurine (Example 15)

5,7-Dimethyl-2-ethyl-3-(2'-(tetrazol-5-yl)biphen-4-
yl)methyl-3H-imidazo[4,5-b]pyridine (Example 16)

25 5,7-Dimethyl-2-propyl-3-(2'-(tetrazol-
5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 17)

30

2-Butyl-5,7-dimethyl-3-(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 18)

5 5-Amino-2-propyl-3-(2'-(tetrazol-5-yl)biphenyl-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 20)

2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 21)

10 2,7-dimethyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 22)

7-Methyl-2-pentyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 23)

15 7-methyl-2-nonyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-methyl-3H-imidazo[4,5-b]pyridine (Example 24)

20 2-Isopropyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 25)

7-Methyl-2-(3-methyl)propyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 26)

25 2-Cyclopropyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 27)

30 2-Methoxymethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 28)

8-Propyl-9-(2'-(tetrazol-5-yl)biphen-4-yl)methylpurine
(Example 29)

5 8-Butyl-6-chloro-9-(2'-(tetrazol-5-yl)biphen-4-yl)methylpurine (Example 30)

8-Butyl-9-(2'-(tetrazol-5-yl)biphen-4-yl)methylpurine
(Example 31)

10 2-Chloro-6-methyl-8-propyl-9-(2'-(tetrazol-5-yl)-biphen-4-yl)methylpurine (Example 32)

2-Dimethylamino-6-methyl-8-propyl-9-(2'-(tetrazol-5-yl)-biphen-4-yl)methylpurine (Example 33)

15 6-Methyl-2-methylamino-8-propyl-9-(2'-(tetrazol-5-yl)-biphen-4-yl)methylpurine (Example 34)

20 6-Methyl-2-(morpholin-4-yl)-8-propyl-9-(2'-(tetrazol-5-yl)biphen-4-yl)methylpurine (Example 35)

7-Methyl-3-(2'-(N-(phenylsulfonyl)carboxamido-biphen-4-yl)methyl-2-propyl-3H-imidazo[4,5-b]pyridine
(Example 37)

25 3-(2'-(N-(4-Chloro)phenylsulfonylcarboxamido)biphen-4-yl)methyl-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine
(Example 38)

30 2-Cyclopropyl-5,7-dimethyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 40)

7-Methyl-2-propyl-3-(2'-trifluoromethylsulfonamido-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
41)

5 7-Methyl-2-propyl-3-(2'-trifluoromethylsulfonamido-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
42, Step 5)

10 5,7-Dimethyl-2-ethyl-3-(2'-trifluoromethylsulfonamido-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
43, Step 3)

15 3-(2'-(N-Acetyl)sulfonamidomethylbiphen-4-yl)methyl-7-
methyl-2-propyl-3H-imidazo[4,5-b]pyridine (Example
43, Step 9)

5-Bromo-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-
4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 44)

20 5-Chloro-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
45)

25 5-Cyano-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
46)

30 5-Carboxy-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
47)

5-(Ethoxycarbonyl)-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo-[4,5-b]pyridine
(Example 48)

5 2-Ethyl-5-(methoxycarbonyl)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo-[4,5-b]pyridine
(Example 49)

10 5-(Benzyloxycarbonyl)-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo-[4,5-b]pyridine
(Example 50)

15 2-Ethyl-5-(iso-propyloxycarbonyl)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo-[4,5-b]pyridine (Example 51)
5-(n-Butyloxycarbonyl)-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo-[4,5-b]pyridine (Example 52)

20 5-Carboxamido-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine
(Example 53)

25 2-Ethyl-7-methyl-5-(morpholin-4-yl)carbonyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine (Example 54)

30 2-Ethyl-7-methyl-5-(isopropyl)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 55)

5-Ethyl-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 56)

5 2-Ethyl-5-(n-hexyl)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 57)

10 2-Ethyl-7-methyl-5-phenyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 58)

15 2-Ethyl-7-methyl-5-(tetrazol-5-yl)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 59)

5-Acetyl-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 60)

20 2-Ethyl-5-((RS)-1-hydroxy)ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 61)

25 2-Ethyl-5-(hydroxymethyl)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 62)

30 2-Ethyl-5-(2-hydroxyprop-2-yl)-7-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 63)

2-Ethyl-5-(3-hydroxypent-3-yl)-7-methyl-3-(2'-(
(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-
b]pyridine (Example 64)

5 5-Amino-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)biphen-
4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example 65)

5-Amino-2-ethyl-7-(trifluoromethyl)-3-(2'-(tetrazol-5-
yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
10 (Example 66)

2-Ethyl-5-(methylamino)-7-methyl-3-(2'-(tetrazol-5-
yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 67)

15 5-(Dimethylamino)-2-ethyl-7-methyl-3-(2'-(tetrazol-5-
yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 68)

20 5-(Methylamino)-2-propyl-3-(2'-(tetrazol-5-yl)-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
69)

5-(Dimethylamino)-2-propyl-3-(2'-(tetrazol-5-yl)-
25 biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
70)

2-Ethyl-5-(hexylamino)-7-methyl-3-(2'-(tetrazol-5-
yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
30 (Example 71)

5-(2-Aminoethyl)amino-2-ethyl-7-methyl-3-(2'-(
(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]-
pyridine (Example 72)

5 5-(Carboxymethyl)amino-2-ethyl-7-methyl-3-(2'-(
(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-
b]pyridine (Example 73)

10 2-Ethyl-7-methyl-5-(4-morpholino)-3-(2'-(tetrazol-5-
yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 74)

15 2-Ethyl-7-methyl-5-(methylthio)-3-(2'-(tetrazol-5-
yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 75)

20 2-Ethyl-5-hydroxy-7-methyl-3-(2'-(tetrazol-5-yl)-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
76)

5-Ethoxy-2-ethyl-7-methyl-3-(2'-(tetrazol-5-yl)-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
77)

25 5-(Acetamidoethyl)amino-2-ethyl-7-methyl-3-(2'-(
(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-
b]pyridine (Example 78)

30 2-Ethyl-5-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-
methyl-3H-imidazo[4,5-b]pyridine (Example 79)

5-Methyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-
methyl-3H-imidazo[4,5-b]pyridine (Example 80)

5 6-Methyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-
methyl-3H-imidazo[4,5-b]pyridine (Example 81)

6-Bromo-7-methyl-2-propyl-3-(2'-(tetrazol-5-yl)-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
82)

10 7-Ethyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-
methyl-3H-imidazo[4,5-b]pyridine (Example 83)

15 7-Isopropyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-
yl)methyl-3H-imidazo[4,5-b]pyridine (Example 84)

7-Ethyl-2-ethyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-
methyl-3H-imidazo[4,5-b]pyridine (Example 85)

20 6-Hydroxymethyl-7-methyl-2-propyl-3-(2'-(tetrazol-5-
yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 86)

25 2-Propyl-7-(p-tolyl)-3-(2'-(tetrazol-5-yl)biphen-4-
yl)methyl-3H-imidazo[4,5-b]pyridine (Example 87)

2-Propyl-7-methyl-6-(p-tolyl)-3-(2'-(tetrazol-5-
yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 88)

30 5-Chloro-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-
methyl-3H-imidazo[4,5-b]pyridine (Example 89)

6-Amino-5,7-dimethyl-2-propyl-3-(2'-(tetrazol-5-yl)-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
90)

5 7-Methyl-2-propyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)-
methyl-3H-imidazo[4,5-b]pyridine-4-oxide (Example 91)

5,7-Dimethyl-6-hydroxy-2-propyl-3-(2'-(tetrazol-5-
yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
10 (Example 92)

5,7-Dimethyl-2-(3,3,3-trifluoroprop-2-yl)-3-(2'-
(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-
b]pyridine (Example 93)

15 2-(3-Butyn-1-yl)-5,7-dimethyl-3-(2'-(tetrazol-5-yl)-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
94)

20 5,7-Dimethyl-2-methyl-3-(2'-(tetrazol-5-yl)biphen-4-
yl)methyl-3H-imidazo[4,5-b]pyridine (Example 95)

7-Chloro-2-ethyl-5-methyl-3-(2'-(tetrazol-5-yl)-
biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine (Example
25 96)

2-Ethyl-5-methyl-7-(4-morpholino)-3-(2'-(tetrazol-5-
yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 97)

30 2-Ethyl-5-methyl-7-(methylamino)-3-(2'-(tetrazol-5-
yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 98)

7-(Dimethylamino)-2-ethyl-5-methyl-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 99)

5 2-Ethyl-5-methyl-7-(methylthio)-3-(2'-(tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 100)

10 5,7-Dimethyl-2-ethyl-3-(4'-chloro-2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine
(Example 101)

15 5,7-Dimethyl-2-ethyl-3-(4'-fluoro-2'-(tetrazol-5-yl)-biphen-4-yl)methyl-3H-imidazo[4,5-b]-pyridine
(Example 102)

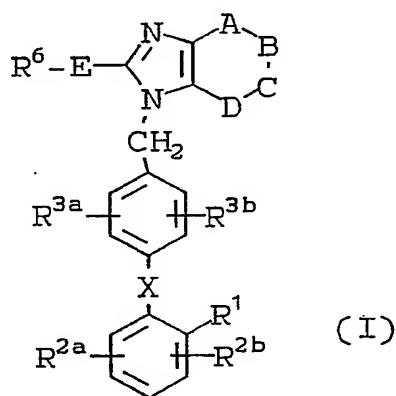
20 5-(Acetoxymethyl)-2-ethyl-7-methyl-3-(2'-tetrazol-5-yl)biphen-4-yl)methyl-3H-imidazo[4,5-b]pyridine
(Example 103)

25

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WHAT IS CLAIMED IS:

1. A method of treating gastrointestinal disorders or central nervous system disorders which comprises administering to a patient in need of such treatment a therapeutically effective amount of a neurotensin antagonist of structural formula:



or a pharmaceutically acceptable salt thereof,

wherein:

R¹ is:

- (a) -NHSO₂R²³,
- (b) -NHSO₂NHCOR²³,
- (c) -NHCONHSO₂R²³,
- (d) -SO₂NHR²³,
- (e) -SO₂NHCOR²³,
- (f) -SO₂NHCONR⁹R²³,
- (g) -SO₂NHCOOR²³,
- (h) -SO₂NHOR²³,

- (i) $-\text{CH}_2\text{SO}_2\text{NHCOR}^{23}$,
- (j) $-\text{CH}_2\text{SO}_2\text{NHCONHR}^{23}$,
- (k) $-\text{CO}_2\text{H}$, or
- (l) $-\text{1H-tetrazol-5-yl}$;

5

R^{2a} and R^{2b} are independently H, Cl, Br, I, F, $-\text{NO}_2$, $-\text{NH}_2$, $\text{C}_1\text{-C}_4\text{-alkylamino}$, $\text{di}(\text{C}_1\text{-C}_4\text{-alkyl})\text{amino}$, $-\text{SO}_2\text{NHR}^9$, CF_3 , $\text{C}_1\text{-C}_4\text{-alkyl}$, or $\text{C}_1\text{-C}_4\text{-alkoxy}$;

10

R^{3a} is

- (a) H,
- (b) Cl, Br, I, F,
- (c) $\text{C}_1\text{-C}_6\text{-alkyl}$,
- (d) $\text{C}_1\text{-C}_6\text{-alkoxy}$,
- (e) $\text{C}_1\text{-C}_6\text{-alkoxyalkyl}$;

15

R^{3b} is

- (a) H,
- (b) Cl, Br, I, F,
- (c) NO_2 ,
- (d) $\text{C}_1\text{-C}_6\text{-alkyl}$,
- (e) $\text{C}_1\text{-C}_6\text{-acyloxy}$,
- (f) $\text{C}_1\text{-C}_6\text{-cycloalkyl}$,
- (g) $\text{C}_1\text{-C}_6\text{-alkoxy}$,
- (h) $-\text{NHSO}_2\text{R}^4$,
- (i) hydroxy $\text{C}_1\text{-C}_4\text{-alkyl}$,
- (j) aryl $\text{C}_1\text{-C}_4\text{-alkyl}$,
- (k) $\text{C}_1\text{-C}_4\text{-alkylthio}$,
- (l) $\text{C}_1\text{-C}_4\text{-alkyl sulfinyl}$,
- (m) $\text{C}_1\text{-C}_4\text{-alkyl sulfonyl}$,
- (n) NH_2 ,

20

25

30

- (o) C₁-C₄-alkylamino,
 (p) C₁-C₄-dialkylamino,
 (q) fluoro C₁-C₄-alkyl,
 (r) -SO₂-NHR⁹,
 5 (s) aryl, or wherein aryl is phenyl or naphthyl
 optionally substituted with one or two
 substituents selected from the group
 consisting of Cl, Br, I, F, C₁-C₄-alkyl,
 C₁-C₄-alkoxy, NO₂, CF₃, C₁-C₄-alkylthio, OH,
 10 NH₂, NH(C₁-C₄-alkyl), N(C₁-C₄-alkyl)₂, CO₂H,
 and CO₂-C₁-C₄-alkyl;
 (t) furyl;

15 R⁴ is H, C₁-C₆ alkyl, aryl or -CH₂-aryl;

R^{4a} is C₁-C₆-alkyl, aryl or -CH₂-aryl;

20 R⁵ is
$$\begin{array}{c} \text{R}^4 \quad \text{O} \\ | \quad || \\ \text{H, -CH-O-C-R}^{4a}; \end{array}$$

E is a single bond, -NR¹³(CH₂)_s-, -S(O)_x-
 (CH₂)_s- where x is 0 to 2 and s is 0 to 5,
 -CH(OH)-, -O-, -CO-;

25 R⁶ is

- (a) aryl unsubstituted or substituted with 1 or
 2 substituents selected from the group
 consisting of Cl, Br, I, F, -O-C₁-C₄-alkyl,
 C₁-C₄-alkyl, -NO₂, -CF₃, -SO₂NR⁹R¹⁰,
 30 -S-C₁-C₄-alkyl, -OH, -NH₂, C₃-C₇-cycloalkyl,
 C₃-C₁₀-alkenyl;

- (b) C₁-C₉-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl
each of which can be unsubstituted or
substituted with a substituent selected from
the group consisting of aryl,
5 C₃-C₇-cycloalkyl, Cl, Br, I, F, -OH, -NH₂,
-NH(C₁-C₄-alkyl), -CF₂CF₃, -N(C₁-C₄-alkyl)₂,
-NH-SO₂R⁴, -COOR⁴, -CF₃, -CF₂CH₃, -SO₂NHR⁹;
or
(c) an unsubstituted, monosubstituted or
10 disubstituted aromatic 5 or 6 membered
cyclic ring which can contain one or two
members selected from the group consisting
of N, O, S, and wherein the substituents are
members selected from the group consisting
15 of -OH, -SH, C₁-C₄-alkyl,
C₁-C₄-alkyloxy, -CF₃, Cl, Br, I, F, or NO₂,
(d) perfluoro-C₁-C₄-alkyl,
(e) C₃-C₇-cycloalkyl optionally mono- or
disubstituted with C₁-C₄-alkyl or -CF₃;

20

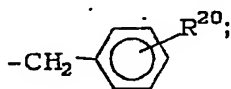
R⁹ is H, C₁-C₅-alkyl, aryl or -CH₂-aryl;

R¹⁰ is H, C₁-C₄-alkyl;

25

R¹¹ is H, C₁-C₆-alkyl, C₂-C₄-alkenyl,
C₁-C₄-alkoxy-C₁-C₄-alkyl, or

30



R¹² is -CN, -NO₂ or -CO₂R⁴;

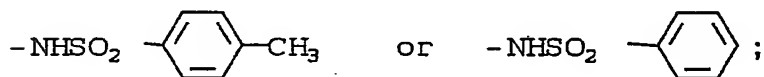
R¹³ is H, -CO(C₁-C₄-alkyl), C₁-C₆-alkyl, allyl,
C₃-C₆-cycloalkyl, phenyl or benzyl;

R¹⁴ is H, C₁-C₈-alkyl, C₁-C₈-perfluoroalkyl,
C₃-C₆-cycloalkyl, phenyl or benzyl;

R¹⁵ is H, C₁-C₆-alkyl;

R¹⁶ is H, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, phenyl or
benzyl;

R¹⁷ is -NR⁹R¹⁰, -OR¹⁰, -NHCONH₂, -NHCSNH₂,



R¹⁸ and R¹⁹ are independently C₁-C₄-alkyl or taken
together are -(CH₂)_q-where q is 2 or 3;

R²⁰ is H, -NO₂, -NH₂, -OH or -OCH₃;

R²² is

(a) phenyl, unsubstituted or substituted with 1
or 2 substituents selected from the group
consisting of: Cl, Br, I, or F, -O-C₁-C₄-
alkyl, C₁-C₄-alkyl, -NO₂, -CF₃, -SO₂NR⁹R¹⁰,
-S-C₁-C₄-alkyl, -OH, -NH₂, -COOR⁴,
C₃-C₇-cycloalkyl, and C₃-C₁₀-alkenyl;

- (b) C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl
each of which is unsubstituted or
substituted with one or more substituents
selected from the group consisting of aryl,
5 C₃-C₇-cycloalkyl, Cl, Br, I, F, -OH,
-O-C₁-C₄-alkyl, -NH₂, -NH(C₁-C₄-alkyl),
-N(C₁-C₄-alkyl)₂, -NH-SO₂R⁴, -COOR⁴,
-SO₂NHR⁹, and -S-C₁-C₄-alkyl;
- (c) an unsubstituted, monosubstituted or
10 disubstituted aromatic 5 or 6 membered ring
comprising one or two heteroatoms selected
from the group consisting of N, O, and S,
and wherein the substituents are members
selected from the group consisting of: -OH,
15 -SH, C₁-C₄-alkyl, C₁-C₄-alkyloxy, -CF₃,
-COOR⁴, Cl, Br, I, F, and NO₂; or
- (d) C₃-C₇-cycloalkyl unsubstituted or
substituted with one or more substituents
selected from the group consisting of:
20 C₁-C₄-alkyl, -O-C₁-C₄-alkyl, -S-C₁-C₄-alkyl,
-OH, -COOR⁴, C₁-C₄-perfluoroalkyl, Cl, Br,
F, and I, or
- (e) (C₁-C₄)-perfluoroalkyl;
- 25 R²³ is
- (a) aryl,
(b) heteroaryl,
(c) C₃-C₄-cycloalkyl,
(d) C₁-C₈-alkyl which can be unsubstituted or
30 substituted with one or two substituents
selected from the group consisting of:

aryl, heteroaryl, wherein heteroaryl is an
 unsubstituted, monosubstituted or
 disubstituted five- or six-membered aromatic
 ring which can optionally contain 1 to 3
 5 heteroatoms selected from the group
 consisting of O, N or S and wherein the
 substituents are members selected from the
 group consisting of: -OH, -SH, -C₁-C₄-alkyl,
 -O(C₁-C₄-alkyl), -S(C₁-C₄-alkyl),
 10 -C₃-C₈-cycloalkyl, -CF₃, Cl, Br, F, I, -NO₂,
 -CO₂H, -CO₂-C₁-C₄-alkyl, -CONR⁴R²²,
 -OCONR⁴R²², -NH₂, -NH(C₁-C₄-alkyl),
 -NHCOR^{4a}, NR⁴COOR⁹ -N(C₁-C₄-alkyl)₂,
 -NR⁴COR²², -NR⁴SO₂R²², -SO₂NR⁴R²², -PO₃H,
 15 -PO(OH)(C₁-C₄-alkyl), -PO(OH)(aryl), or
 -PO(OH)(O-C₁-C₄-alkyl), or
 (e) perfluoro-C₁-C₄-alkyl;

X is absent or is

- 20 (a) a carbon-carbon single bond,
 (b) -CO-,
 (c) -O-,
 (d) -S-,
 (e) $\begin{array}{c} \text{-N-} \\ | \\ \text{R}^{13} \end{array}$
 25 (f) $\begin{array}{c} \text{-CON-} \\ | \\ \text{R}^{15} \end{array}$
 (g) $\begin{array}{c} \text{-NCO-} \\ | \\ \text{R}^{15} \end{array}$

30

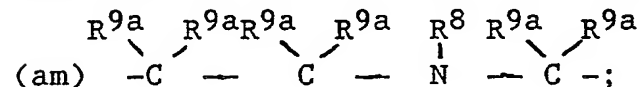
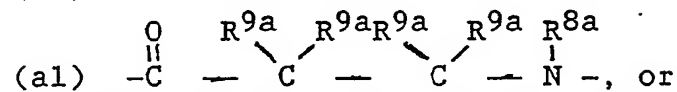
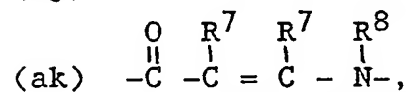
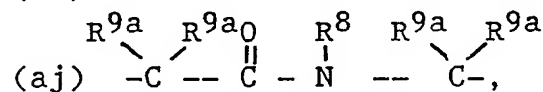
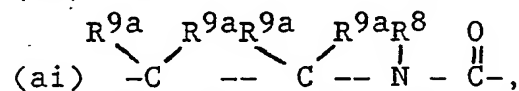
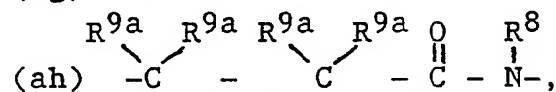
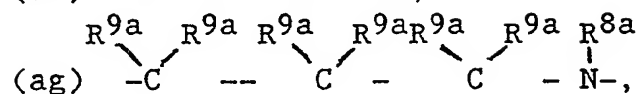
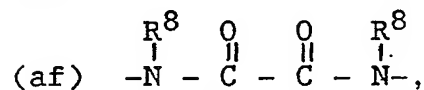
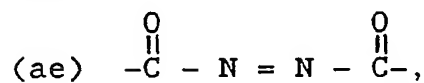
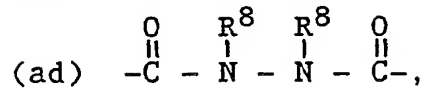
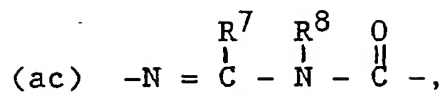
- (h) $-\text{OCH}_2-$,
 (i) $-\text{CH}_2\text{O}-$
 (j) $-\text{SCH}_2-$,
 (k) $-\text{CH}_2\text{S}-$,
 5 (l) $-\text{NHC}(\text{R}^9)(\text{R}^{10})$,
 (m) $-\text{NR}^9\text{SO}_2-$,
 (n) $-\text{SO}_2\text{NR}^9-$,
 (o) $-\text{C}(\text{R}^9)(\text{R}^{10})\text{NH}-$,
 (p) $-\text{CH}=\text{CH}-$,
 10 (q) $-\text{CF}=\text{CF}-$,
 (r) $-\text{CH}=\text{CF}-$,
 (s) $-\text{CF}=\text{CH}-$,
 (t) $-\text{CH}_2\text{CH}_2-$,
 (u) $-\text{CF}_2\text{CF}_2-$,
 15 (v) $-\overset{\text{CH}_2}{\underset{\text{CH}}{\text{C}}}-$ and $\text{>}\overset{\text{CH}_2}{\underset{\text{CH}_2}{\text{C}}}$,
 20 (w) $-\overset{\text{OR}^{14}}{\underset{\text{CH}}{\text{C}}}-$,
 (x) $-\overset{\text{OCOR}^{14}}{\underset{\text{CH}}{\text{C}}}-$,
 25 (y) $-\overset{\text{NR}^{17}}{\underset{\text{C}}{\text{C}}}-$, or
 30 (z) $-\overset{\text{R}^{18}\text{O}}{\underset{\text{NR}^{17}}{\text{C}}}-$;

Z is O, NR¹³ or S;

-A-B-C-D- represents the constituent atoms of a 6-member carbocycle or a 6-member saturated or unsaturated heterocyclic ring with the imidazole to which they are attached containing 1 to 3 nitrogen atoms and includes the following:

- (a) $\begin{array}{cccc} R^7 & R^7 & R^7 & R^7 \\ | & | & | & | \\ -C & = C & - C & = C-, \end{array}$
- (b) $\begin{array}{cccc} R^7 & R^7 & R^7 & \\ | & | & | & \\ -C & = C & - C & = N-, \end{array}$
- (c) $\begin{array}{cccc} & R^7 & R^7 & R^7 \\ & | & | & | \\ -N & = C & - C & = C-, \end{array}$
- (d) $\begin{array}{cccc} R^7 & R^7 & & R^7 \\ | & | & & | \\ -C & = C & - N & = C-, \end{array}$
- (e) $\begin{array}{cccc} R^7 & & R^7 & R^7 \\ | & & | & | \\ -C & = N & - C & = C-, \end{array}$
- (f) $\begin{array}{cccc} R^7 & R^7 & & \\ | & | & & \\ -C & = C & - N & = N-, \end{array}$
- (g) $\begin{array}{cccc} & & R^7 & R^7 \\ & & | & | \\ -N & = N & - C & = C-, \end{array}$
- (h) $\begin{array}{cccc} R^7 & & & R^7 \\ | & & & | \\ -C & = N & - N & = C-, \end{array}$
- (i) $\begin{array}{cccc} & R^7 & R^7 & \\ & | & | & \\ -N & = C & - C & = N-, \end{array}$
- (j) $\begin{array}{cccc} & R^7 & & R^7 \\ & | & & | \\ -N & = C & - N & = C-, \end{array}$
- (k) $\begin{array}{cccc} R^7 & & R^7 & \\ | & & | & \\ -C & = N & - C & = N-, \end{array}$

- (1) $\text{-N} = \text{N} - \text{N} = \overset{\text{R}^7}{\underset{|}{\text{C}}}\text{-},$
- (m) $\overset{\text{R}^7}{\underset{|}{\text{C}}} = \text{N} - \text{N} = \text{N-},$
- 5 (n) $\text{-N} = \text{N} - \overset{\text{R}^7}{\underset{|}{\text{C}}} = \text{N-},$
- (o) $\text{-N} = \overset{\text{R}^7}{\underset{|}{\text{C}}} - \text{N} = \text{N-},$
- 10 (p) $\begin{array}{cccc} \text{O} & \text{R}^8 & \text{O} & \text{R}^8 \\ || & | & || & | \\ \text{-C} & - \text{N} & - \text{C} & - \text{N-}, \end{array}$
- (q) $\begin{array}{cccc} \text{R}^8 & \text{O} & \text{R}^8 & \text{O} \\ | & || & | & || \\ \text{-N} & - \text{C} & - \text{N} & - \text{C-}, \end{array}$
- (r) $\begin{array}{cccc} \text{R}^7 & \text{R}^7 & \text{O} & \text{R}^8 \\ | & | & || & | \\ \text{-C} & = \text{C} & - \text{C} & - \text{N-}, \end{array}$
- 15 (s) $\begin{array}{cccc} \text{R}^8 & \text{O} & \text{R}^7 & \\ | & || & | & \\ \text{-N} & - \text{C} & - \text{C} & = \text{N-}, \end{array}$
- (t) $\begin{array}{cccc} \text{R}^7 & \text{O} & \text{R}^8 & \\ | & || & | & \\ \text{-N} & = \text{C} & - \text{C} & - \text{N-}, \end{array}$
- 20 (u) $\begin{array}{cccc} \text{R}^7 & \text{R}^7 & \text{O} & \text{R}^8 \\ | & | & || & | \\ \text{-C} & = \text{C} & - \text{C} & - \text{N-}, \end{array}$
- (v) $\begin{array}{cccc} \text{R}^7 & \text{R}^7 & \text{R}^8 & \text{O} \\ | & | & | & || \\ \text{-C} & = \text{C} & - \text{N} & - \text{C-}, \end{array}$
- (w) $\begin{array}{cccc} \text{R}^8 & \text{O} & \text{R}^7 & \text{R}^7 \\ | & || & | & | \\ \text{-N} & - \text{C} & - \text{C} & = \text{C-}, \end{array}$
- 25 (x) $\begin{array}{cccc} \text{O} & \text{R}^8 & \text{R}^7 & \text{R}^7 \\ || & | & | & | \\ \text{-C} & - \text{N} & - \text{C} & = \text{C-}, \end{array}$
- (y) $\begin{array}{cccc} \text{R}^8 & \text{O} & & \\ | & || & & \\ \text{-N} & - \text{C} & - \text{N} & = \text{N-}, \end{array}$
- 30 (z) $\begin{array}{cccc} & \text{O} & \text{R}^8 & \\ & || & | & \\ \text{-N} & = \text{N} & - \text{C} & - \text{N-}, \end{array}$
- (aa) $\begin{array}{cccc} \text{O} & \text{R}^8 & & \\ || & | & & \\ \text{-C} & - \text{N} & - \text{N} & = \text{N-}, \end{array}$
- (ab) $\begin{array}{cccc} \text{O} & \text{R}^8 & \text{R}^7 & \\ || & | & | & \\ \text{-C} & - \text{N} & - \text{C} & = \text{N-}, \end{array}$



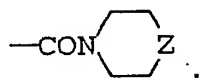
R^7 groups can be the same or different and represent:

- a) hydrogen,
- b) C_1-C_6 straight or branched chain alkyl, or C_2-C_6 alkenyl, or alkynyl each of which is unsubstituted or substituted with:

i) $-OH$

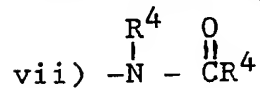
- ii) C₁-C₄-alkoxy,
- iii) -CO₂R⁴,
- iv) -OCOR⁴,
- v)

5



- vi) -CON(R⁴)₂

10



- viii) -N(R⁴)₂,

- ix) aryl as defined above,

- x) heterocyclic as defined in (p) below,

15

- xi) -S(O)_xR²³,

- xii) tetrazol-5-yl,

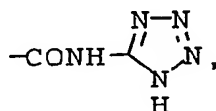
- xiii) -CONHSO₂R²³,

- xiv) -SO₂NH-heteroaryl,

- xv) -SO₂NHCOR²³,

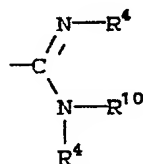
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- xvi)



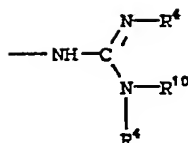
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- xvii)



30

xviii)



5

xix) $\text{---PO(OR}^4\text{)}_2$,

xx) $\text{---PO(OR}^4\text{)R}^9$,

10

c) Cl, Br, I, F,

d) perfluoro-C₁-C₄-alkyl,

e) -OH,

f) -NH₂,

g) ---N---R^{23} ,

15

$|$
R⁴

h) ---N---COR^{23} ,

$|$
R⁴

i) -OR²³,

j) -CO₂R⁴,

20

k) -CON(R⁴)₂,

l) -NH-C₃-C₇-cycloalkyl,

m) C₃-C₇-cycloalkyl,

n) aryl as defined above, or

o) heterocyclic which is a five- or six-

25

membered saturated or unsaturated ring
containing up to three heteroatoms selected
from the group consisting of O, N or S

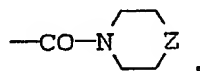
wherein S may in the form of sulfoxide or
sulfone and which may be optionally

30

substituted with one or two substituents
which are members selected

from the group consisting of halo(Cl, Br, F, I), C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-S(O)_x- where x is as defined above, CF₃, NO₂, OH, CO₂H, CO₂-C₁-C₄-alkyl, or -N(R⁴)₂;

- 5 p) -CN,
- q) (CH₂)_nN- wherein n is 4 to 6,
- r) -SO₂N(R⁴)₂;
- s) tetrazol-5-yl,
- t) -CONHSO₂R²³,
- 10 u) -PO(OR⁴)₂,
- v) -NHSO₂CF₃,
- w) -SO₂NH-heteroaryl,
- x) -SO₂NHCOR²³,
- y) -S(O)_x-R²³,
- 15 z)

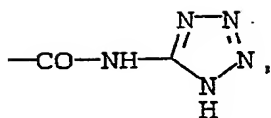


- 20 aa) -PO(OR⁴)R⁹,
- bb) -NHSO₂R²³,
- cc) -NHSO₂NHR²³,
- dd) -NHSO₂NHCOR²³,
- ee) -NHCONHSO₂R²³,
- 25 ff) -N(R⁴)CO₂R²³,
- gg) $\begin{array}{cc} \text{R}^4 & \text{R}^4 \\ | & | \\ -\text{N}-\text{CON}-\text{R}^{23}, \end{array}$

hh) -CO-aryl,

ii)

5



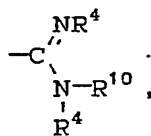
jj) -CO-C₁-C₄-alkyl,

10

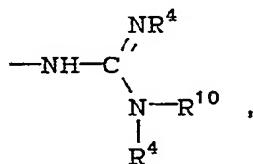
kk) -SO₂NH-CN,

ll)

15



mm)



20

R⁸ groups can be the same or different and represent:

a) hydrogen,

b) C₁-C₆-alkyl or alkenyl either unsubstituted or substituted with hydroxy, C₁-C₄-alkoxy, -N(R⁴)₂, -CO₂R⁴, or C₃-C₅-cycloalkyl;

c) C₃-C₅-cycloalkyl,

R^{8a} is R⁸ or C₁-C₄-acyl;

30

R^{9a} groups can be the same or different and represent:

- a) hydrogen,
- b) C₁-C₆-alkyl either unsubstituted or substituted with
 - i) hydroxy,
 - ii) -CO₂R⁴,
 - iii) -CONHR⁴, or
 - iv) -CON(R⁴)₂.

2. The method of Claim 1, wherein:

R¹ is:

- (a) -NHSO₂R²³,
- (b) -NHSO₂NHCOR²³,
- (c) -NHCONHSO₂R²³,
- (d) -SO₂NHR²³,
- (e) -SO₂NHCOR²³,
- (f) -SO₂NHCONR⁹R²³,
- (g) -SO₂NHCOOR²³,
- (h) -SO₂NHOR²³,
- (i) -CH₂SO₂NHCOR²³,
- (j) -CH₂SO₂NHCONHR²³, or
- (k) -1H-tetrazol-5-yl;

X is a single bond;

R^{2a} and R^{2b} are independently:

- (a) C₁-C₄-alkyl,
- (b) halogen,
- (c) hydrogen;

R^{3a} and R^{3b} are independently:

- (a) C₁-C₆-alkyl,
- (b) halogen, or
- (c) C₁-C₆-alkoxy,
- (d) hydrogen;

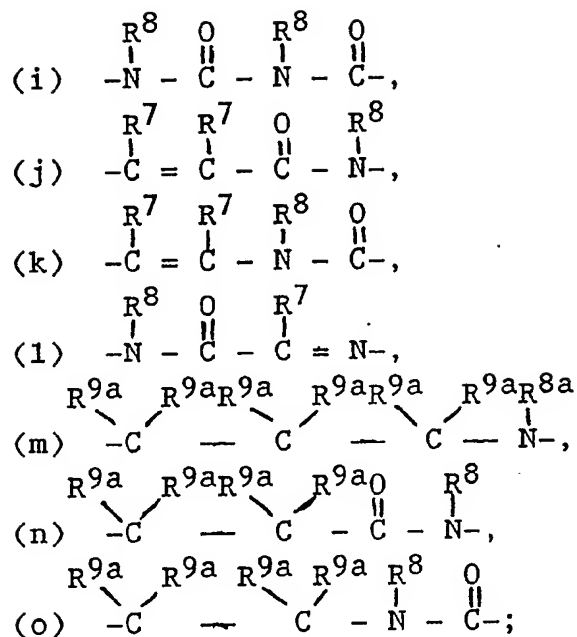
R⁴ is H, or C₁-C₄-alkyl;

E is a single bond or -S-;

R⁶ is a branched or straight chain C₁-C₆-alkyl,
C₃-C₇-cycloalkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl
each of which is either unsubstituted or
substituted with C₁-C₄-alkylthio, C₁-C₄-alkoxy,
CF₃, CF₂CF₃ or -CF₂CH₃;

A-B-C-D- represents:

- (a) $\begin{array}{cccc} R^7 & R^7 & R^7 & R^7 \\ | & | & | & | \\ -C & = & C & - C = C-, \end{array}$
- (b) $\begin{array}{cccc} R^7 & R^7 & R^7 & \\ | & | & | & \\ -C & = & C & - C = N-, \end{array}$
- (c) $\begin{array}{cccc} R^7 & R^7 & & R^7 \\ | & | & & | \\ -C & = & C & - N = C-, \end{array}$
- (d) $\begin{array}{cccc} & R^7 & & R^7 \\ & | & & | \\ -N & = & C & - N = C-, \end{array}$
- (e) $\begin{array}{cccc} R^7 & & R^7 & \\ | & & | & \\ -C & = & N & - C = N-, \end{array}$
- (f) $\begin{array}{cccc} & R^7 & R^7 & \\ & | & | & \\ -N & = & C & - C = N-, \end{array}$
- (g) $\begin{array}{cccc} R^7 & R^7 & & \\ | & | & & \\ -C & = & C & - N = N-, \end{array}$
- (h) $\begin{array}{cccc} O & R^8 & O & R^8 \\ || & | & || & | \\ -C & - & N & - C - N-, \end{array}$



R^7 groups are the same or different and represent:

- (a) hydrogen,
- (b) $-\text{C}_1-\text{C}_4$ -alkyl, either unsubstituted or substituted with:
 - i) $-\text{OH}$,
 - ii) $-\text{CO}_2\text{R}^4$,
 - iii) $-\text{NH}_2$,
 - iv) $(\text{C}_1-\text{C}_4 \text{ alkyl})\text{amino}$,
 - v) $\text{di}(\text{C}_1-\text{C}_4\text{-alkyl})\text{amino}$,
- (c) Cl, Br, I, F,
- (d) $-\text{CF}_3$,
- (e) $-\text{OH}$,
- (f) $-\text{N}(\text{R}^4)_2$,
- (g) $-\text{C}_1-\text{C}_4$ -alkoxy,
- (h) $-\text{CO}_2\text{R}^4$,
- (i) $-\text{CONH}_2$,

- (j) -C₃-C₇-cycloalkyl,
- (k) aryl,
- (l) heterocyclic as defined above,
- (m) -CF₃,
- (n) tetrazol-5-yl,
- (o) -CONHSO₂R²³,;

R⁸ groups are the same or different and represent,

- (a) hydrogen,
- (b) C₁-C₄-alkyl either unsubstituted or substituted with -OH or -CO₂R⁴; and

R^{8a} represents

- (a) hydrogen,
- (b) C₁-C₄ alkyl, or
- (c) (C₁-C₄-alkyl)CO-; and

R^{9a} groups are the same or different and represent:

- (a) hydrogen,
- (b) C₁-C₄-alkyl.

3. The method of Claim 1 wherein:

R¹ is:

- (a) -SO₂NHCOR²³,
- (b) -SO₂NHCONR⁹R²³,
- (c) -SO₂NHCOOR²³,
- (d) -SO₂NHOR²³,
- (e) -CH₂SO₂NHCOR²³, or
- (f) -1H-tetrazol-5-yl;

R^{2a} and R^{2b} are independently:

- (a) C₁-C₄-alkyl,
- (b) chloro, or
- (c) hydrogen;

5

R^{3a} and R^{3b} are independently:

- (a) C₁-C₄-alkyl,
- (b) chloro, or
- (c) C₁-C₄-alkoxy, or
- (d) hydrogen;

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E is a single bond or -S-;

R⁶ is

15

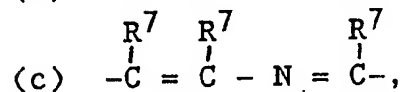
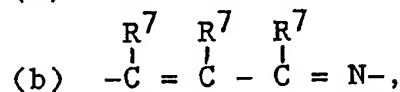
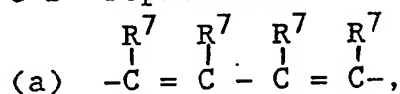
- (a) a branched or straight chain C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl each of which is either unsubstituted or substituted with C₁-C₄-alkylthio, C₁-C₄-alkoxy, CF₃, CF₂CF₃ or -CF₂CH₃;

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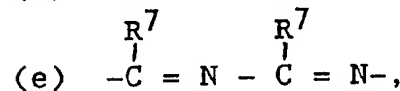
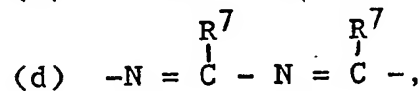
- (b) C₃-C₇-cycloalkyl;
- (c) perfluoro-C₁-C₄-alkyl;

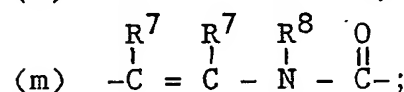
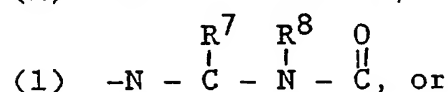
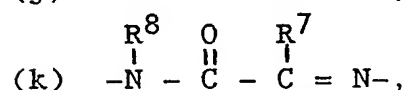
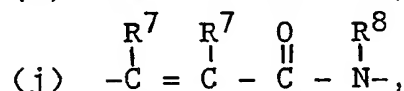
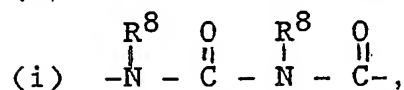
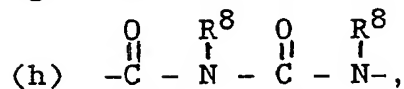
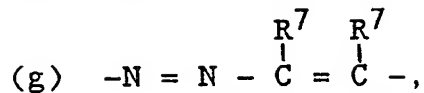
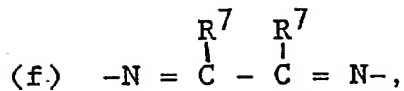
A-B-C-D- represents:

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R^7 groups are the same or different and represent:

(a) hydrogen,

(b) $-C_1-C_4$ -alkyl, either unsubstituted or substituted with $-OH$ or $-CO_2R^4$,

(c) Cl, Br, I, or F,

(d) $-OH$,

(e) $-N(R^4)_2$,

(f) $-C_1-C_4$ -alkoxy, or

(g) $-CO_2R^4$,

(h) aryl,

(i) heterocyclic as defined above,

(j) $-CF_3$,

(k) tetrazol-5-yl,

R^8 groups are the same or different and represent:

- (a) H,
- (b) C_1-C_4 -alkyl either unsubstituted or substituted with $-OH$ or $-CO_2R^4$.

5

4. The compound of Claim 3 wherein:

R^1 is:

- 10 (a) $-SO_2NHCOR^{23}$,
- (b) $-SO_2NHCONR^9R^{23}$,
- (c) $-SO_2NHCOOR^{23}$,
- (d) $-SO_2NHOR^{23}$,
- (e) $-CH_2SO_2NHCOR^{23}$, or
- 15 (f) $-1H-tetrazol-5-yl$;

E is a single bond;

A-B-C-D represents:

- 20 (a) $\begin{array}{cccc} R^7 & R^7 & R^7 & R^7 \\ | & | & | & | \\ -C & = & C & - & C & = & C- \end{array}$,
- (b) $\begin{array}{cccc} R^7 & R^7 & R^7 & \\ | & | & | & \\ -C & = & C & - & C & = & N- \end{array}$,
- 25 (c) $\begin{array}{cccc} R^7 & & R^7 & \\ | & & | & \\ -C & = & N & - & C & = & N- \end{array}$ or
- (d) $\begin{array}{cccc} R^7 & R^7 & O & R^8 \\ | & | & || & | \\ -C & = & C & - & C & - & N- \end{array}$.

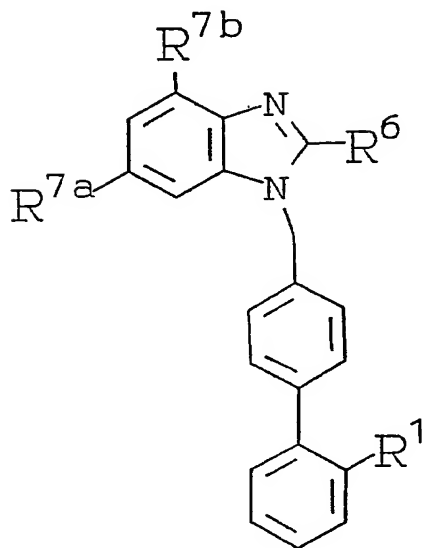
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5. The method of Claim 4 wherein the compound is selected from the group consisting of:

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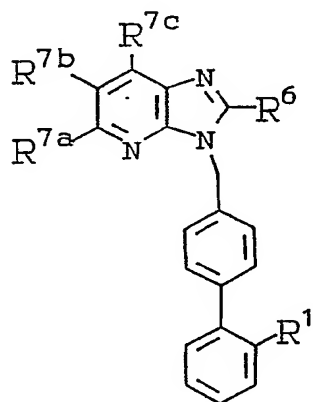
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<u>R¹</u>	<u>R⁶</u>	<u>R^{7a}</u>	<u>R^{7b}</u>
SO ₂ NHCO-Ph	ethyl	methyl	methyl
SO ₂ NHCO-4-pyridyl	ethyl	methyl	methyl
SO ₂ NHCO-propyl	ethyl	methyl	methyl
SO ₂ NHCO-n-heptyl	ethyl	methyl	methyl
SO ₂ NHCOCH ₂ CH ₂ -cyclopentyl	ethyl	methyl	methyl
SO ₂ NHCO-(3-aminophenyl)	ethyl	methyl	methyl
SO ₂ NHCOCH ₂ NHBoc	ethyl	methyl	methyl
SO ₂ NHCO(CH ₂) ₅ NH ₂	ethyl	methyl	methyl
SO ₂ NHCO(CH ₂) ₅ NHBoc	ethyl	methyl	methyl
SO ₂ NHCOCH ₂ NH ₂	ethyl	methyl	methyl
SO ₂ NHCO-(4-methoxyphenyl)	ethyl	methyl	methyl

	SO ₂ NHCO-cyclopropyl	ethyl	CO ₂ Me	methyl
	SO ₂ NHCO-(4-aminophenyl)	ethyl	CO ₂ Me	methyl
	SO ₂ NHCOCH ₂ CH ₂ CO-N-morpholinyl	ethyl	methyl	methyl
	SO ₂ NHCO-2-thienyl	ethyl	CO ₂ Me	methyl
5	SO ₂ NHCO(CH ₂) ₅ NHBoc	ethyl	CO ₂ Me	methyl
	SO ₂ NHPO(obenzy1) ₂	ethyl	methyl	methyl
	SO ₂ NHCOCF ₂ Cl	ethyl	methyl	methyl
	SO ₂ NHSO ₂ -N-methyl-N-piperidinyl	ethyl	methyl	methyl
	SO ₂ NHCO ₂ CH ₂ CH ₃	ethyl	methyl	methyl
10	SO ₂ NHCO(CH ₂) ₃ NH ₂	ethyl	methyl	methyl
	SO ₂ NHCO-3-aminophenyl	ethyl	CO ₂ Me	methyl
	SO ₂ NHCO-4-dimethylamino	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₅ NHBoc	cyclopropyl	methyl	methyl
	SO ₂ NHCO-4-tolyl	ethyl	methyl	methyl
15	SO ₂ NHCO(CH ₂) ₄ CO ₂ Et	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₄ CO ₂ H	ethyl	methyl	methyl
	SO ₂ NHCO-phenyl	cyclopropyl	methyl	methyl
	SO ₂ NHCO-N-morpholinyl	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₅ N(CH ₃) ₂	ethyl	methyl	methyl
20	SO ₂ NHCO(CH ₂) ₅ NH ₂	ethyl	methyl	methyl
	SO ₂ NHCO-4-(N-t-butoxycarbonyl-piperidinyl)	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₂ CH(NHBoc)(CO ₂ t-Bu)	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₆ NH ₂	ethyl	methyl	methyl
25	SO ₂ NHCO-cyclopropyl	ethyl	CH ₂ OH	methyl
	SO ₂ NHCO-2-thiazolyl	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₃ NHt-Boc	ethyl	methyl	methyl
	SO ₂ NHCO(CH ₂) ₃ NHt-Boc	ethyl	methyl	methyl
30	SO ₂ NHCO-cyclopropyl	ethyl	CON(CH ₃) ₂	methyl.

6. The method of Claim 4 wherein the compound is selected from the group consisting of:



R₁

R₆

R_{7a}

R_{7b}

R_{7c}

SO ₂ NHCOphenyl	ethyl	methyl	bromine	methyl
tetrazol-5-yl	butyl	methyl	N(benzyl)CObutyl	H
tetrazol-5-yl	butyl	methyl	NHCON(phenyl) ₂	H.

7. The method of Claim 1 wherein the gastrointestinal disorder is selected from the group consisting of gastroesophagal reflux disorder (GER D), irritable bowel syndrome, diarrhea, cholic,
5 ulcer, GI tumors, dyspepsia, pancreatitis, esophagitis and gastroparesis.

8. A pharmaceutical composition useful in the treatment of gastrointestinal disorders which
10 comprises a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound as recited in Claim 1.

9. The method of Claim 1 wherein the
15 central nervous disorder is selected from the group consisting of psychoses, depression, cognitive dysfunction, and anxiety, tardive dyskinesia, drug dependency, panic attack and mania.

20 10. A pharmaceutical composition useful in the treatment of central nervous system disorders which comprises a pharmaceutically acceptable carrier and a pharmaceutically acceptable amount of a
25 compound as recited in Claim 1.

11 The use of a compound as defined in any of claims 1-6 in the preparation of a medicine for the
30 treatment of a condition as defined in any of claims 1, 7 or 10.